REVIEW

Tachycardia-Induced Cardiomyopathy

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ABSTRACT

Tachycardia-induced cardiomyopathy (TIC) is characterized by reversible left ventricular (LV) dysfunction caused by long-standing tachycardia. The diagnosis of TIC is challenging due to lack of guidelines and specific assessment tools. Advanced imaging and endomyocardial biopsy should be taken into consideration in the future as contributors in the diagnostic process.

There are numerous unknowns to TIC, the most pressing being the lack of diagnostic and prognostic tools. The presence of persistent negative LV remodeling after the normalization of the LV ejection fraction with adequate treatment of the tachycardia gives us a glimpse into the complex pathophysiologic processes at play, as well as the disease prognosis.

Keywords: Tachycardia-induced cardiomyopathy, left ventricular dysfunction, supraventricular tachycardia, atrial fibrillation, atrial flutter, premature ventricular contractions.

REZUMAT

Cardiomiopatia tahiaritmică este caracterizată prin disfuncție ventriculară stângă reversibilă, determinată de tahicardie persistentă. Diagnosticul este o provocare prin lipsa ghidurilor și a mijloacelor de evaluare specifice. Imagistica avansată și biopsia endomiocardică ar trebui luate în considerare ca viitoare opțiuni utile în procesul de evaluare și diagnostic.

Sunt numeroase necunoscute în ceea ce privește cardiomiopatia tahiaritmică, cele mai notabile derivate tocmai din absența criteriilor și investigațiilor care să ducă la un diagnostic de certitudine. Remodelarea negativă a ventriculului stâng după normalizarea fracției de ejecție în urma tratamentului ne poate oferi indicii legate de complexitatea procesului fiziopatologic precum și în ceea ce privește prognosticul cardiomiopatiei tahiaritmice.

Cuvinte cheie: cardiomiopatie tahiaritmică, disfuncție ventriculară stângă, tahicardie supraventriculară, fibrilație atrială, extrasistole ventriculare.

INTRODUCTION

Tachycardiomyopathy or tachycardia-induced cardiomyopathy (TIC) is a cause of left ventricular (LV) dysfunction, which is generally considered to be reversible. TIC has been documented in the setting of incessant or persistent supraventricular or ventricular tachyarrhythmias. Adequate control of the incriminating tachyarrhythmia can result in the improvement or complete resolution of the LV dysfunction.

It is important to define and differentiate two categories: arrhythmia-induced TIC, when the ventricular dysfunction can be attributed to the arrhythmia, without any other underlying condition, and arrhythmia-mediated TIC, when another structural heart disease is identified in the patient[1].

However, TIC remains an elusive entity, with a yet to be fully elucidated pathophysiologic mechanism, risk factors and prognosis. To date, echocardiography is the main imaging technique used in the diagnosis of LV dysfunction and it is essential for the differential diagnosis in TIC. Other imaging techniques, such as cardiac magnetic resonance (CMR), can further aid in the exclusion of other etiologies and assist in therapeutic decisions.

PATHOPHYSIOLOGY

TIC can be caused by a diversity of tachyarrhythmias, such as atrial fibrillation (AF), atrial flutter, incessant supraventricular tachycardia, ventricular tachycardia (VT) and frequent ventricular premature beats (VPB). Table I summarizes the common categories and types of tachycardia associated with TIC[2]. However, most of the knowledge on how these arrhythmias cause LV dysfunction comes from animal studies, where LV dysfunction was induced with rapid ventricular or atrial pacing[3,4]. While it seems reasonable that the animal

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models previously mentioned could shed a light on the pathophysiologic mechanisms of TIC in humans, it is also clear that they are imperfect. Since it is a known fact that right ventricular pacing, at normal rates, can have detrimental effects on the human heart[5], the animal models using atrial pacing are probably closer to the spontaneous arrhythmias causing TIC than those using fast right ventricular pacing.

Various structural and hemodynamic changes have been reported in response to rapid atrial and ventricular pacing. The most important are LV dilation and impaired systolic and diastolic LV function[6,7]. LV cavity dilation is not generally accompanied by LV hypertrophy in TIC[8]. As a consequence of LV dilation, mitral regurgitation can also develop and contribute to further dilation of the LV. There are many studies that showed the role of the mitral valve annulus in mitral regurgitation in patients with dilated cardiomyopathies, but also the role of the leaflets per se. In TIC, the altered mechanical loads were shown to affect the matrix synthesis and remodeling of the mitral valve, influencing its structure and function. Moreover, the degree of LV remodeling itself, as measured by percent changes in end diastolic volume, end-systolic volume and LVEF in TIC was in strong correlation with leaflet changes[9].

On a cellular level, the changes found in animal models of TIC include loss of myocytes, alteration of the extracellular matrix, with reduced adhesion of the myocyte to the basement membrane and abnormal collagen composition, that determine increased LV stiffness and impaired contractility[10]. Furthermore, changes in the distribution of capillaries have been found, with consequent myocardial blood flow impairment, resulting in myocardial ischemia and worsening of LV impairment[11].

On a molecular level, there is evidence of reduced myocardial energy stores, decreased activity of the Na-K-ATPase pump and decreased mitochondrial activity[4,12]. Moreover, important abnormalities of the calcium channel activity in the sarcoplasmic reticulum have been shown, ultimately affecting the excitation-contraction coupling[12].

Other known contributing changes in TIC are downregulation of beta-adrenergic receptors and increased levels of oxidative stress[14]. Finally, neurohormonal changes have been observed in TIC, similar to those encountered in other forms of heart failure. There is a certain activation of the renin-angiotensin-aldosterone pathways, resulting in high levels of atrial natriuretic peptide, angiotensin II and aldosterone, with myocardial fibrosis as the result[14].

In a recent retrospective study reported by Mueller et al.[15], biopsy samples taken from patients diagnosed with TIC showed a decrease in myofibril numbers, abnormal nuclear membranes, macrophages infiltration and less myocardial fibrosis compared with dilated cardiomyopathy (DCM) and inflammatory cardiomyopathy.

One of the important conclusions is that TIC has histological and biochemical aspects that are different from other cardiomyopathies, so if the changes identified can be reproduced in future studies, endomyocardial biopsy could become a useful tool in the final diagnosis of TIC. Furthermore, the fact that some microscopic changes are irreversible has been emphasized[15], implying that an early intervention could result in a more favorable outcome.

Although PVC do not represent an actual tachycardia, it has been proven that it is a category indeed responsible for TIC. PVCs were thought to be benign. However, in the last decade, cardiomyopathy due to frequent PVCs in healthy hearts is now recognized.

The mechanism of PVC-mediated cardiomyopathy is not fully understood. There have been animal simulations in which pacing protocols simulating PVCs produce a form of TIC that resolved completely within 2 to 4 weeks. The tissue did not have inflammation, fibrosis or apoptosis, but potential mechanisms are - true rate-related cardiomyopathy due to higher average heart rates, dyssynchrony (reducing global cardiac mechanical efficiency, asymmetrically increased wall thickness in the late-activated regions), especially when left bundle block morphology, abnormal ventricular filling or abnormal Calcium handling. Nonetheless, the most important factor predicting TIC is the daily burden of PVC >10.000 PVCs/day, while reducing the number to <5000 PVCs/ day can be a target when eliminating them is not possible[52]. Other predictors were wider PVCs, epicardial origin, retrograde P waves.[54]

DIAGNOSIS AND IMAGING

One of the major challenges in the diagnosis of TIC is the lack of specific investigations that can confirm the diagnosis. TIC is essentially an exclusion diagnosis. Reversal of LV dysfunction upon adequate control of the tachycardia is the key feature for differentiating TIC from DCM and other cardiomyopathies.

Table 1. Types of tachyarrhythmias associated with TIC. Adapted from Khanis et al.[2]

Conditions that can induce TIC
Supraventricular causes
Atrial fibrillation
Atrial flutter
Atrial tachycardia
Atrioventricular reentrant tachycardia
Atrioventricular nodal reentrant tachycardia
Permanent form of junctional
Persistent junctional reciprocating tachycardia
Ventricular causes
Premature ventricular complexes (PVC)
Right ventricular outflow tract ventricular tachycardia
Idiopathic left ventricular tachycardia
Bundle-branch reentry ventricular tachycardia
Ventricular pacing at high rates
Extracardiac causes
Thyrotoxicosis
Glucagonoma

A clinical suspicion of TIC should be raised whenever encountering a patient with newly diagnosed LV dysfunction and a tachyarrhythmia, with no alternate diagnosis. However, in those with previously known LV dysfunction with a different etiology, a persistent tachyarrhythmia could be responsible for a further decline in the LV ejection fraction (LVEF) and the diagnosis of TIC should not be disregarded. There are no established cut-offs for heart rate or duration of the tachyarrhythmia causing TIC, but it is reasonable to take into consideration TIC in patients with heart rate above 100 bpm, with tachyarrhythmias occurring in a persistent or recurrent paroxysmal manner[16]. There is a need for criteria that can predict the occurrence of TIC in those experiencing tachyarrhythmias.

The classic presentation in TIC is congestive heart failure (HF) in the presence of a tachyarrhythmia. It should be noted that the patients may not have arrhythmia at the time of examination, but TIC should be suspected if an arrhythmia has been previously documented[1].

Echocardiography is the main imaging technique used in the evaluation of any patient presenting with HF symptoms, because of its availability and cost-efficiency. The echocardiographic evaluation of patients with TIC does not identify any pathognomonic signs, however some imaging particularities of this patient population have been documented. Patients with TIC are known to have a smaller LV end-diastolic diameters and LV volumes when adjusted for body surface area (BSA) compared to patients with idiopathic DCM at the initial time of presentation[17]. Furthermore, LV end-diastolic dimensions have been found to be independent predictors for TIC in the same study by Jeong et al.[17]. An additional finding is the lower LV mass index of patients with TIC, compared to patients with idiopathic DCM. These echocardiographic findings are significant, and given the appropriate clinical context, should raise the suspicion of TIC, but are insufficient to confirm the diagnosis. Other findings that could support such a suspicion are evidence of previously normal LV function, lack of other risk factors for cardiomyopathy (untreated hypertension, alcohol abuse etc.) and most importantly, the recovery of the LV after adequate rhythm or rate control1. However, since the presence of an underlying structural disease does not exclude TIC and a persistent tachycardia could worsen an already depressed LV function, TIC should be suspected if the degree of LV dysfunction is out of proportion to the severity of the comorbidities[18].

If the above-mentioned criteria are met (Figure 1), aggressive management of the causative tachycardia should be initiated, whether it is a rate control strategy or a rhythm control strategy. It is generally expected to document improvement or complete resolution of LV dysfunction within 4-12 weeks once the tachyarrhythmia is addressed[19].

Even though it has been shown that most echocardiographic changes tend to improve after the tachyarrhythmia is controlled, there is proof that patients with TIC have higher stroke volume and LV end-systolic diameter compared to the normal population, even after the improvement of the LVEF[18]. It is important

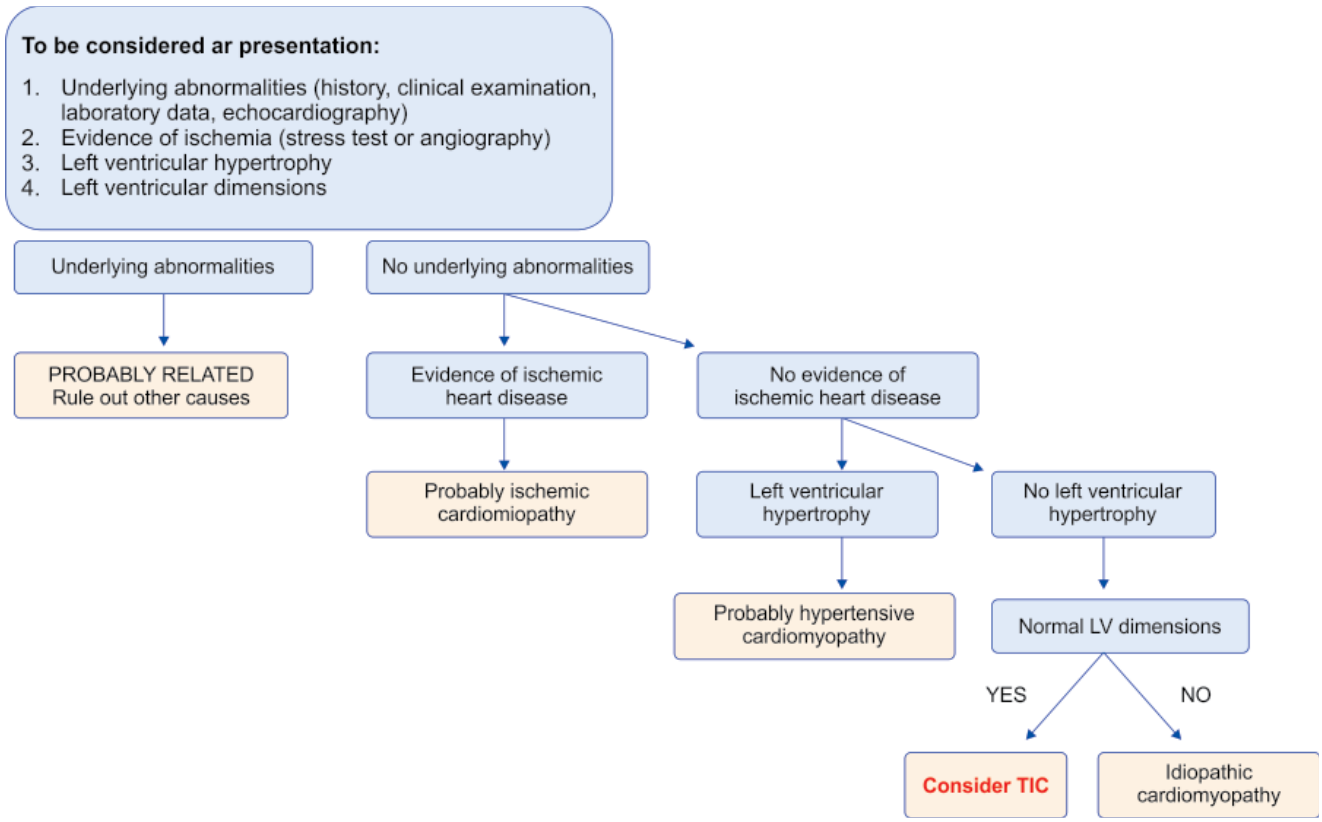

Figure 1. Etiologic differential diagnosis of heart failure with tachycardia. Adapted from Jeong, et al.[17]

to note that this finding is consistent with the findings in animal models of TIC[16], which show persistent histologic changes in the myocardium. These changes might suggest a more long-lasting impact of TIC, despite treatment of the tachycardia, with possible consequences on prognosis.

However, most of the echocardiographic assessments in studies followed very few parameters and it is important to take into consideration a more detailed analysis of the LV. A future perspective of imaging in TIC should be broadening the panel of measurements performed in order to gain a better understanding of the disease. Kusunose et al.[20] attempted to better characterize the course of TIC, by using advanced echocardiographic techniques to predict the functional recovery in LV systolic function. LV size, LVEF and E/e' at baseline evaluation predicted improvement of LVEF during follow-up. More importantly, strain distribution was the most powerful independent predictor of improvement in LV function in this study. Further studies using this technique on a larger population are needed to establish its long-term prognostic value.

Although most of the studies that aimed TIC had focused the echocardiographic evaluation around LV systolic function, in clinical practice - where diastolic dysfunction plays an increasing important role, tools of such evaluation should be taken into consideration in patients with TIC as well. When analyzing the myocardial tissue, after LV biopsy samples were obtained, prepared and electrically paced, it has been proven that tachycardia plays an important part in distolic dysfunction, and that tachycardia-induced incomplete relaxation was associated with increase LV mass and left atrial volumes.[55] This can be a promising start to a more adequate measurement of LV relaxation pattern in patients with TIC.

Since left atrium (LA) size is one of the parameters used in diastolic dysfunction quantification, LA remodeling could be of interest for evaluation and prognosis. LA remodeling (defined by increasing volume >15% compared to baseline) is the result of either electrical remodeling consequent to persistent supraventricular tachycardia or secondary to increased LV end- diastolic pressure[46]. Although specific measuring and moni-

toring LA remodeling is not yet part of the guidelines, it is important to keep in mind that LA indexed volume >34/ml/m^2 and LA strain <31% had a 2-fold and 4-fold hazard increase for patients with paroxysmal AF to develop persistent AF in the next 26 months[47]. This is of great importance when managing patients with TIC, in order to better assess visits frequency, prognosis or therapeutic approach. Moreover, reverse modelling of LA volume after pulmonary vein isolation had also demonstrated a lower AF reccurence[48].

MRI techniques can be useful in identifying different patterns of fibrosis, suggesting certain pathologies. Late gadolinium enhancement (LGE) has been scarcely studied in TIC, as its presence is generally considered to be caused by an altogether different pathology, that is responsible for the LV dysfunction. However, since there is consistent proof that structural changes are present in TIC, LGE could be interpreted in the context of TIC for certain patients. Tomodori et al.[21] found diffuse LV LGE in a patient with TIC in the context of Wolff Parkinson White and recurrent paroxysmal AF. On two months follow-up, after the ablation of the accessory pathway, there was compete resolution of the LV dysfunction, as well as the LGE, as shown on CMR. On the other hand, Can et al.[22] found that LGE is a rare in patients with TIC caused by idiopathic ventricular arrhythmias. These findings might support further studies into the morphologic changes of TIC, depending on the causing arrhythmia. Moreover, LGE could be useful in predicting the recovery of LV function in patients with TIC. The CAMERA-MRI study[23] aimed to determine whether catheter ablation (CA) for AF could improve LVEF in patients with TIC and no other suspected underlying etiology for LV dysfunction. The investigators concluded that CA was superior to adequate rate control. The presence of LGE on MRI predicted a worse outcome post-ablation, with an inverse correlation between the extent of LGE and the magnitude of LV recovery post CA.

THERAPEUTIC APPROACH

It is important to acknowledge the fact that patients with TIC have better outcomes compared to those with DCM. There is undeniable data that supports the fact that restoring sinus rhythm, controlling ventricular response and decreasing the number PVCs will lead to improvement of LV function. The therapeutic approach must be adapted to each patient, but initiation of classic heart failure medication is important and should not be delayed.

Supraventricular arrhythmias

The most frequently encountered supraventricular arrhythmia causing TIC is atrial fibrillation. Both rhythm control strategy and rate control strategy have been shown to be effective in these patients.

Randomized studies demonstrated the positive effect of sinus rhythm restoration on LV remodeling for patients with TIC and AF. In a recent trial - AATAC-AF[24] (*Ablation vs Amiodarone for Treatment of ATrial Fibrillation in Patients With Congestive Heart Failure and an Implanted ICD/CRTD*), that randomized 203 patients with persistent AF and LV dysfunction to amiodarone or catheter ablation (CA), 70% of patients in the ablation arm were free of AF (vs 34% in the amiodarone arm ($p<0.001$)) and had significant improvement in mortality, hospitalization rates and quality of life. Restoration and maintenance of sinus rhythm is an important determinant of recovery of LV function.

On the other hand, several trials, such as AFFIRM[25], RACE26, PAF 1-2[27,28] and STAF[29] have shown that rate control it is a valid and comparable option in terms of mortality, but smaller studies stated the hypothesis that rhythm control may be superior in terms of LV remodeling. The CAMERA- MRI study showed significant improvement of LV function in patients with suspicion of TIC, who were treated with CA, compared to those who achieved adequate rate control[23]. The superiority of rhythm control with CA in this setting could be explained by the fact that mechanisms other than a high heart rate are at play, such as irregular ventricular activity and loss of atrial contraction[30].

Pulmonary Vein Isolation, meaning complete electrical isolation of the pulmonary veins, can be achieved either surgically or by radiofrequency(RF) ablation. Patients with heart failure and cardiomyopathy who have atrial fibrillation may benefit form RF ablation[40].In such study, it has been noted an important improvement of mean LVEF (35% to 56%) in patients with heart failure. The most relevant improvement could be seen after 3 months. Moreover, 92% of the patients without adequate rate control who previously did not have structural heart disease, had a final increase of more than 20% in LVEF.[40] This is a clear clue that whenever possible, pulmonary vein isolation must pe taken into consideration in patients with atrial fibrillation and TIC.

AV node ablation, with ventricular pacing can be a valid choice when the patient cannot tolerate medication or when drugs are insufficient for rate control. A meta-analysis that included more than 2000 patients with node ablation showed not only important

improvement of cardiac function but better quality of life as well[41]. The ones that had a bigger benefit were patients with LVEF <45%. Besides the regression of cardiomyopathy per se, the possibility of administering negative inotropes with increasing ventricular filling time was also of great value. Nonetheless it should always be taken into consideration that right ventricular pacing can lead to regional motion abnormalities and adverse haemodynamics.

When comparing AV Node Ablation vs Pulmonic Vein Isolation - prospective randomized trial of 81 patients, it could be seen that pulmonic vein isolation lead to a bigger increase in LVEF (35% vs 28%), a better quaility of life and a lower incidence of progressive atrial fibrillation[42].

The available data suggests that catheter ablation is the best answer for rhythm control in patients with AF- mediated TIC[51].

Regarding atrial flutter, a recent publication by Oka et al.[31] on the subject of TIC management, comparing rate control versus rhythm control concluded that rhythm control strategy had better results in terms of LVEF recovery. Strict rate control should be an alternative if rhythm control is not available.

Radiofrequency ablation proved its efficacy, especially because atrial flutter's rate is more difficult to control - so, taking this into consideration and high success in ablation with low risk of complications during the procedure, ablation to eliminate atrial flutter is recommended[51]. A study performed in over 100 patients with atrial flutter (not necessarily with TIC) showed significantly improvement of LV function (57%) while in 75% of the patients LV function improved to normal. Moreover, in half of the patients, an ICD (initially indicated) was no longer needed[44]. Tachycardia-induced cardiomyopathy may be a more common mechanism of LV dysfunction in patients with atrial flutter that expected, and aggressive treatment of this arrhythmia should be considered[45].

Incessant atrial tachycardia and reentrant supraventricular tachycardias are rare causes of TIC, however they should not be disregarded in the setting of LV dysfunction of unknown etiology. When considering supraventricular tachycardias resulting in TIC, a curative strategy by catheter ablation should be pursued whenever possible as first-line therapy for supraventricular mediated-TIC51. Successful CA can normalize LVEF and has promising long-term prognosis. As Medi et al.[50] showed when enrolling 345 consecutive patients with focal atrial tachycardia - long term restoration of LV function can be achieved after successful catheter ablation of the tachycardia focus.

Ventricular arrhythmias

Ventricular arrhythmias causing TIC are generally idiopathic, such as those arising from the outflow tracts or the aortic cusps. The most common presentation involves frequent PVCs, with sustained ventricular tachycardia being a rare phenomenon.

When managing ventricular arrhythmias and TIC myocardial dysfunction is an important limiting factor regarding medication in patients with ventricular arrhythmias - Class IA and IC agents cannot be used because of their pro-arrhythmia, while class IV agents can negatively influence the clinical status. The only agent that can 'safely' be used is amiodarone - although its non-cardiac effects can limit its use as well. Considering the difficulty of managing TIC with antiarrhymic drugs and the fact that the affected myocardium involved is usually localized, RF ablation is considered as an effective therapy[43].

Recently, criteria for PVC-induced cardiomyopathy have been elaborated. Del Carpio Munoz et al.[33] suggest that otherwise young healthy individuals, without abnormal cardiovascular substrate having over 20 000 PVCs per day, no more than two PVC morphologies, and with preserved myocardial wall thickness are the best candidates for presumption of a PVC-induced cardiomyopathy diagnosis. Ventricular function can improve if the PVC burden is reduced to <5000/ day[34]. There are various studies that have evaluated the possibility of predicting TIC in patients with PVCs based on PVC burden, most of them concluding that a percentage between 10% and 25% is detrimental[35]. There is evidence showing that PVCs with a QRS width >150 ms are also more likely to result in TIC[36].

Although PVC are not a form of tachycardia pers se , it is important to mention that - catheter ablation is considered the definitive therapy for PVC-mediated TIC, with succes rates raging from 70% to 90%. Elimination improved LVEF, ventricular dimensions and even mitral regurgitation[52]. A recent study reported that more than a quarter of patients had improvement in the LV function at 1 week following ablation, and those with early improvement had a greater total improvement in LV function at 1 year[49].

RECCURENCE AND PROGNOSIS

Patients who experience TIC are prone to recurrence of LV systolic dysfunction with a faster and more severe onset than the initial presentation, if the same

or another tachycardia occurs. There are several small studies showing the rapid decline in LVEF in those experiencing recurrent tachycardia, after a diagnosis of TIC[37,38]. This could be explained by the persistent negative remodeling of the LV found in several studies, after apparent normalization of LVEF, suggesting persistent structural myocardial abnormalities. The most important implication is that treatment and follow-up of patients who had TIC must be very carefully managed and heart failure treatment could be necessary for a longer duration, even after LVEF normalization[39].

The prognosis of TIC is generally favorable with adequate control of the tachycardia. However, it is probably reasonable to suspect that a risk of malignant ventricular arrhythmias exists in the presence of LV dysfunction. It is unclear at this moment whether a risk of sudden death persists after normalization of LVEF. There are scarce reports of sudden death in patients with TIC and a normalized LVEF in the literature[37]. Furthermore, another important unknown is the risk of sudden death in those who experience recurrence of TIC, which is generally associated with a more abrupt decline in LVEF. In conclusion, there is urgent need for studies to determine reliable risk prognosis tools for the patient population with TIC.

CONCLUSIONS

Tachycardia induced cardiomyopathy is an elusive diagnosis, that requires a high degree of clinical suspicion, an individually tailored approach and a very thorough follow-up.

Echocardiography is an important tool in the diagnosis of TIC, however a high level of clinical suspicion is essential. Further studies using advanced echocardiographic techniques and CMR in TIC are necessary to identify possible specific changes related to the disease. Moreover, CMR could prove to have an important role in guiding the treatment in patients with a suspicion of TIC. Another investigation of interest in the future is endomyocardial biopsy, as it could help clarify the diagnosis and aid in the characterization of the disease.

Further studies into the pathophysiologic mechanisms, risk factors and prognosis of TIC are of paramount importance.

Compliance with ethics requirements:

The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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