Curr Heart Fail Rep (2013) 10:296–306
DOI 10.1007/s11897-013-0150-z

PREVENTION OF HEART FAILURE (M ST. JOHN SUTTON, SECTION EDITOR)

Heart Failure and Tachycardia-Induced Cardiomyopathy

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Published online: 21 August 2013

Abstract Congestive heart failure is a major health care concern affecting almost six million Americans and an estimated 23 million people worldwide, and its prevalence is increasing with time. Long-standing tachycardia is a well-recognized cause of heart failure and left ventricular dysfunction and has led to the nomenclature, tachycardia-induced cardiomyopathy. Tachycardia-induced cardiomyopathy is generally a reversible cardiomyopathy with effective treatment of the causative arrhythmia, either with medications, surgery, or catheter ablation. Tachycardia-induced cardiomyopathy remains poorly understood and is likely underdiagnosed. A better understanding of tachycardia-induced cardiomyopathy and improved recognition of its presence in clinical practice is vital to the health of patients with this disorder. The goal of this review is to discuss the pathogenesis and clinical manifestations of tachycardia-induced cardiomyopathy, as well as approaches to its diagnosis and treatment.

Keywords Tachycardia-induced cardiomyopathy · Tachycardia-mediated cardiomyopathy · Congestive heart failure · Supraventricular tachycardia · Atrial fibrillation · Cardiomyopathy · Premature ventricular contractions · Premature ventricular depolarizations · Ventricular tachycardia

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Abbreviations

CHF	Congestive heart failure
TIC	Tachycardia-induced cardiomyopathy
LV	Left ventricle
AF	Atrial fibrillation
SVT	Supraventricular tachycardia
VT	Ventricular tachycardia
PVCs	Premature ventricular contractions
AV	Atrioventricular
AT	Atrial tachycardia
AVNRT	Atrioventricular nodal reentrant tachycardia
AVRT	Atrioventricular reciprocating tachycardia
PJRT	Persistent junctional reciprocating tachycardia
LVEF	Left ventricular ejection fraction
AADs	Antiarrhythmic drugs

Introduction

Congestive heart failure (CHF) is a major health care concern affecting almost six million Americans and an estimated 23 million people worldwide, and its prevalence is increasing with time [1, 2]. Heart failure management requires significant healthcare resource utilization, and the epidemic is expected to grow in the years to come [3]. Long-standing tachycardia is a well-recognized cause of heart failure and left ventricular (LV) dysfunction and has led to the nomenclature, tachycardia-induced cardiomyopathy (TIC). TIC is generally a reversible cardiomyopathy with effective treatment of the causative arrhythmia, either with medications, surgery, or catheter ablation. The diagnosis is usually made after demonstrating recovery of LV function with normalization of arrhythmia in the absence of other identifiable etiologies. Despite being a known cause of cardiomyopathy for the last 100 years [4], TIC remains a poorly understood phenomenon that is likely under-diagnosed. A better understanding of TIC and improved recognition of its presence in clinical practice is vital to the

health of patients with this disorder. The goal of this review is to discuss the pathogenesis and clinical manifestations of TIC as well as approaches to its diagnosis and treatment.

Pathophysiology

Most of what is known about the underlying pathophysiology of TIC is based on the results of animal studies, primarily in dogs and pigs, where heart failure was induced with sustained rapid atrial or ventricular pacing [5–9]. It is important to recognize that these animal models are only an approximation of the pathophysiology of TIC in humans. It is well known that atrial and ventricular pacing, even at physiologic heart rates, have been associated with increased rates of heart failure [10], and various forms of abnormal ventricular activation can adversely effect LV function, including chronic right ventricular pacing [11–13], left bundle branch block [14, 15], and ventricular pre-excitation [16, 17]. With these limitations in mind, a model of heart failure utilizing rapid atrial pacing is likely a close approximation to the physiology of heart failure in the setting of spontaneous arrhythmias.

Various structural and hemodynamic changes have been reported as a response to sustained rapid atrial or ventricular pacing (Table 1). These changes include markedly elevated LV filling pressures [18–20], impaired ventricular contractile function [9, 20–23], reduced cardiac output, elevated systemic vascular resistance [6, 7, 18, 22], increased LV wall stress [22, 24–26], abnormal diastolic function [27], and LV cavity dilatation [18–20, 25, 28]. Commonly, LV cavity dilation is accompanied by little or no change in LV wall mass with a normal or reduced LV wall thickness [8, 19]. Mitral regurgitation has also been seen, likely as a result of an increase in LV dimensions, which may contribute to further LV dilation and dysfunction [18]. Cellular changes include loss of myocytes, cellular elongation, myofibril misalignment, and derangements in the extracellular matrix with reduced myocyte attachment to the basement membrane [9, 29]. As a response to these changes, similar to other forms of CHF, pacing-induced CHF in animal models results in upregulation of the neurohormonal axis, leading to elevated levels of serum atrial natriuretic peptide, renin, aldosterone, angiotensin-II, epinephrine, and norepinephrine [30, 31].

Myocardial energy store depletion, reduced myocardial blood flow, increased oxidative stress, impaired beta adrenergic responsiveness, and abnormal calcium handling have all been implicated in the pathogenesis of TIC. Reduced myocardial energy stores have been shown with decreased levels of creatine, phosphocreatine, adenosine triphosphate, and glycogen, enhanced activity of Krebs cycle oxidative enzymes, decreased activity of the Na-K-ATPase pump, and mitochondrial injury with decreased mitochondrial activity [5, 9, 23, 32]. Increased levels of oxidative stress have been demonstrated and have been associated with higher degrees of myocyte apoptosis. Treatment with antioxidants has been shown to decrease oxidative stress, myocyte injury, and apoptosis and attenuate cardiac dysfunction [33, 34]. Changes in the structure, distribution, and function of the coronary vasculature in TIC have been demonstrated, including abnormal subendocardial and subepicardial blood flow ratios and impaired coronary flow reserve [35, 36]. These changes may impair myocardial blood flow and limit oxygen delivery, accelerating myocardial injury, and worsening ventricular dysfunction. Downregulation of beta-adrenergic receptors and a resultant decreased sympathetic responsiveness [37, 38] independent of hemodynamic and neurohormonal factors [39] has also been described and has been shown to normalize in the setting of rate control [40]. Extensive abnormalities in calcium channel activity and calcium transport in the sarcoplasmic reticulum have been seen as early as 24 hours after the initiation of rapid pacing, with the severity of calcium cycling abnormalities correlating with the degree of ventricular dysfunction, potentially through abnormal excitation-contraction coupling [23, 41].

Table 1 Pathophysiologic changes in animal models of tachycardia-induced cardiomyopathy

Hemodynamic changes
Depressed left ventricular function
Elevated left ventricular filling pressures
Impaired ventricular contractile function
Reduced cardiac output
Elevated systemic vascular resistance
Increased left ventricular wall stress
Left ventricular diastolic dysfunction
Mitral regurgitation
Structural changes
Left ventricular cavity dilation
Subendocardial fibrosis
Normal or reduced left ventricular wall thickness
Reduced myocardial blood flow
Cellular changes
Myocyte elongation
Increased oxidative stress
Myocyte hypertrophy
Extracellular matrix/basement membrane disruption
Myofibril alignment disruption
Reduced myocardial energy stores
Mitochondrial dysfunction
Down-regulation of beta adrenergic receptors
Abnormal calcium handling
Increased myocyte apoptosis
Neurohormonal changes
Increased renin, aldosterone, angiotensin-II, epinephrine, norepinephrine, ANP, BNP

What is not clear regarding the proposed mechanisms described above is whether these changes contribute to myocardial dysfunction, or are merely a result of increased myocardial demands from rapid pacing and decreased myocardial supply due to elevated ventricular filling pressures and decreased cardiac output. Many of the changes reported above are not unique to TIC, but are seen in multiple forms of heart failure and may be related, at least in part, to the downstream effects of elevated filling pressures and decreased cardiac output rather than the tachycardia itself.

Time Course and Recovery

Variable accounts of TIC recovery have been reported in the literature. The most rigorous studies in this regard again rely on animal models of TIC. Hemodynamic abnormalities have been shown to develop as early as 24 hours after the initiation of rapid pacing. Increased intracardiac filling pressures, increased pulmonary artery pressures, and decreased systemic arterial pressures generally plateau at 1 week, whereas cardiac output, ejection fraction, and cardiac volumes may continue to worsen for up to 3 to 5 weeks [18, 20, 28, 30]. Changes in intracardiac filling pressures, cardiac output, and systemic vascular resistance are generally reversible with cessation of rapid pacing, although in some cases, ejection fraction may not return to baseline and abnormalities in contractile function may persist. [28, 42] Within 48 hours of cessation of pacing, intracardiac filling pressures, systemic arterial pressures, systemic vascular resistance, and cardiac index have been shown to return to levels similar to control animals [24]. Although significant improvements in left ventricular ejection fraction (LVEF) have been seen by 24 to 48 hours, complete normalization may not be seen for several weeks [21, 24], and residual contractile dysfunction in isolated myocytes has been seen for up to 4 weeks [43]. Within 4 weeks, all hemodynamic variables generally return to control levels, while end-systolic and end-diastolic volumes may remain elevated 12 weeks after termination of pacing [21, 22, 28, 44]. LV hypertrophy has been shown to develop after the cessation of rapid pacing, although the mechanism of this hypertrophy is not well understood [43–45], and has not been reproducibly reported in humans.

Associated Arrhythmias

Multiple arrhythmias have been associated with TIC, including atrial fibrillation (AF), atrial flutter, incessant supraventricular tachycardia (SVT), ventricular tachycardia (VT), and premature ventricular contractions (PVCs) (Table 2). Restoration of sinus rhythm, control of the ventricular response, or decrease in the frequency of premature contractions all result in an improvement in LV function and clinical heart failure.

Table 2 Causative arrhythmias of tachycardia-induced cardiomyopathy

Supraventricular
Atrial fibrillation
Atrial flutter
Incessant atrial tachycardia
Permanent junctional reciprocating tachycardia
AV nodal reentrant tachycardia (rare)
AV reentrant tachycardia (rare)
1:2 Non-reentrant dual AV nodal tachycardia
Ventricular
Ventricular tachycardia
Premature ventricular contractions
Other
Persistent right ventricular pacing
Persistent rapid atrial pacing
Left bundle branch block
Ventricular pre-excitation

AV = atrioventricular

TIC can occur at any age and has been reported as early as in utero [46], but can also be seen in infants, children [47–49], and adults. The true incidence of TIC is unknown, given that most reports in the literature are small retrospective series or cases studies involving individual patients. Estimations of incidence are also limited by the fact that TIC is a diagnosis of exclusion and no single test can be performed to confirm or refute its presence. TIC is likely an under-diagnosed phenomenon, with the true incidence being higher than what has been reported thus far in the literature.

Supraventricular Arrhythmias

The most rigorously studied etiology of TIC in human subjects is chronic AF. AF is known to increase risk of heart failure irrespective of the heart failure etiology [50]. LV function has been shown to improve with multiple AF treatment strategies, including rate control, rhythm control with cardioversion, antiarrhythmic drugs, or catheter ablation, and an ablate and pace strategy. The pathogenesis of TIC in the setting of AF is not well understood, but goes beyond atrial contractile function, atrioventricular (AV) synchrony, and elevated heart rates alone. Improvement in LV function has been shown to lag behind return of atrial contractile function [51], and patients treated with AV junction ablation and permanent ventricular pacing have shown improvement in LV function irrespective of their atrial rhythm and function [52–56]. Patients have been shown to have abnormal LV function in the setting of chronic AF and controlled ventricular rates with normalization of LV function following AV junction ablation, suggesting that regularity and not rate alone are important in TIC, at least in some patients [57]. Similar results have been published in patients

with AF treated with catheter ablation, where only a minority of the patients with depressed LV function had elevated ventricular rates on routine monitoring prior to ablation [58•]. Atrial flutter has also been associated with the development of TIC and a recent study of patients with atrial flutter reported that 25 % had LV dysfunction prior to ablation, and that 57 % of those patients had significantly improved LV function following ablation. In 75 % of those patients, LV function completely normalized [59•].

Atrial fibrillation is the most commonly study arrhythmia related to TIC, not only because of its prevalence in the general population, but also because of its chronicity, an important requisite of any tachycardia likely to cause TIC. Incessant atrial tachycardia (AT), as opposed to paroxysmal atrial tachycardia, is a relatively uncommon SVT, but is a well-known cause of TIC and tends to be related to increased automaticity of an ectopic atrial pacemaker [60]. Rates are frequently related to a patient's level of alertness and activity, and may increase during pregnancy since the ectopic focus tends to be sensitive to autonomic modulation. Surgery [61–63] and catheter ablation [64, 65] have been utilized to treat incessant AT with subsequent improvement in LV function in the majority of patients. The most recent series of incessant AT patients reported normalization of LV function in 97 % of patients after successful ablation [66•].

Reentrant SVTs, including atrioventricular nodal reentrant tachycardia (AVNRT) and atrioventricular reciprocating tachycardia (AVRT), are generally paroxysmal, and therefore rarely cause TIC except when they are incessant in nature. The latter category would include persistent junctional reciprocating tachycardia (PJRT), a form of incessant AVRT and a well-known cause of TIC. Since they are less common, incessant reentrant SVTs are also less well studied, but TIC has been reported in the setting of AVNRT, AVRT, and PJRT [67–70]. It is important to recognize that although PJRT is most commonly associated with a slowly conducting septal accessory pathway; slowly conducting accessory pathways can found anywhere on the annuli, and some cases of TIC due to AVRT reported in the literature may have been better classified as PJRT variants. As is the case with all forms of TIC, definitive treatment of the causative arrhythmia with pharmacologic suppression [71], surgery [67, 68], or catheter ablation [68–70] results in reversal of LV dysfunction.

Although it is rare for AVNRT to become incessant, dual AV nodal physiology can facilitate the development of TIC through an incessant form of nonreentrant AV nodal tachycardia. In this scenario, a single sinus beat may result in two ventricular depolarizations with double antegrade conduction via fast and slow AV nodal pathways [72]. 1:2 tachycardia occurs when this phenomenon repeats with such frequency that tachycardia ensues. In a recent review of the literature, 44 cases of 1:2 nonreentrant dual AV nodal tachycardia were described between 1970 and 2010. Of these, eight patients had a reduced LVEF <45 %. All eight of these patients underwent catheter ablation of the slow AV nodal pathway, with subsequent normalization of LV function in all cases. A ninth patient was reported to have normalization of LV dysfunction after rate control alone [73•].

Ventricular Arrhythmias

Sustained monomorphic ventricular tachycardia less commonly causes TIC as compared to SVTs, since sustained VT is most often associated with some form of underlying structural heart disease. When ventricular tachycardia does lead to TIC, it is by definition idiopathic and most commonly originates from the right ventricular outflow tract, LV outflow tract, or coronary cusps. If these arrhythmias become persistent or repetitive enough, they may cause reversible LV dysfunction (Fig. 1) [74–76]. A recent single center series reported that 11 % of patients who presented with frequent PVCs also had sustained monomorphic VT and 7 % of those patients had TIC. The presence of repetitive monomorphic VT was a significant predictor of TIC development, particularly when it was the predominant arrhythmia on 24-hour Holter monitoring [77•]. As is the case with supraventricular arrhythmias, LV dysfunction generally normalizes following ablation of the arrhythmia [75, 76, 78].

The most active area of recent research in the field of TIC has been focused on the effects of PVCs on LV function. PVCs have been associated with the development of TIC in the absence of sustained ventricular arrhythmias, and the severity of TIC is generally related to the burden of ventricular ectopy [77•, 79•, 80, 81]. True tachycardia may not be present in this setting, despite development of cardiomyopathy suggesting that, as is the case with AF, other factors must play a role in the development of LV dysfunction beyond heart rate alone. It has been postulated that electrical activation originating within the ventricular myocardium due to PVCs causes a dysynchronous, inefficient mechanical ventricular contraction. With time, this may lead to LV dysfunction through remodeling effects. As with idiopathic ventricular tachycardia, idiopathic PVCs have a predilection for the outflow tracts and coronary cusps, although the development of TIC is thought to be irrespective of the PVC origin [82•, 83•]. Yet, it was recently reported that TIC is less frequently seen in patients with PVCs from the right ventricle and more frequently seen with PVCs originating from the epicardium [84•].

Several studies have shown that PVC frequency correlates with extent of LV dysfunction. Patients with decreased LVEF at the time of presentation have been found to have a higher mean PVC burden as compared to those with normal LV function [79•, 81, 86]. However, a clearly defined cut-off at which time TIC is likely to develop has not been determined. Some studies have focused on PVC burden as a percent of total ventricular activations, while others have examined the absolute number of

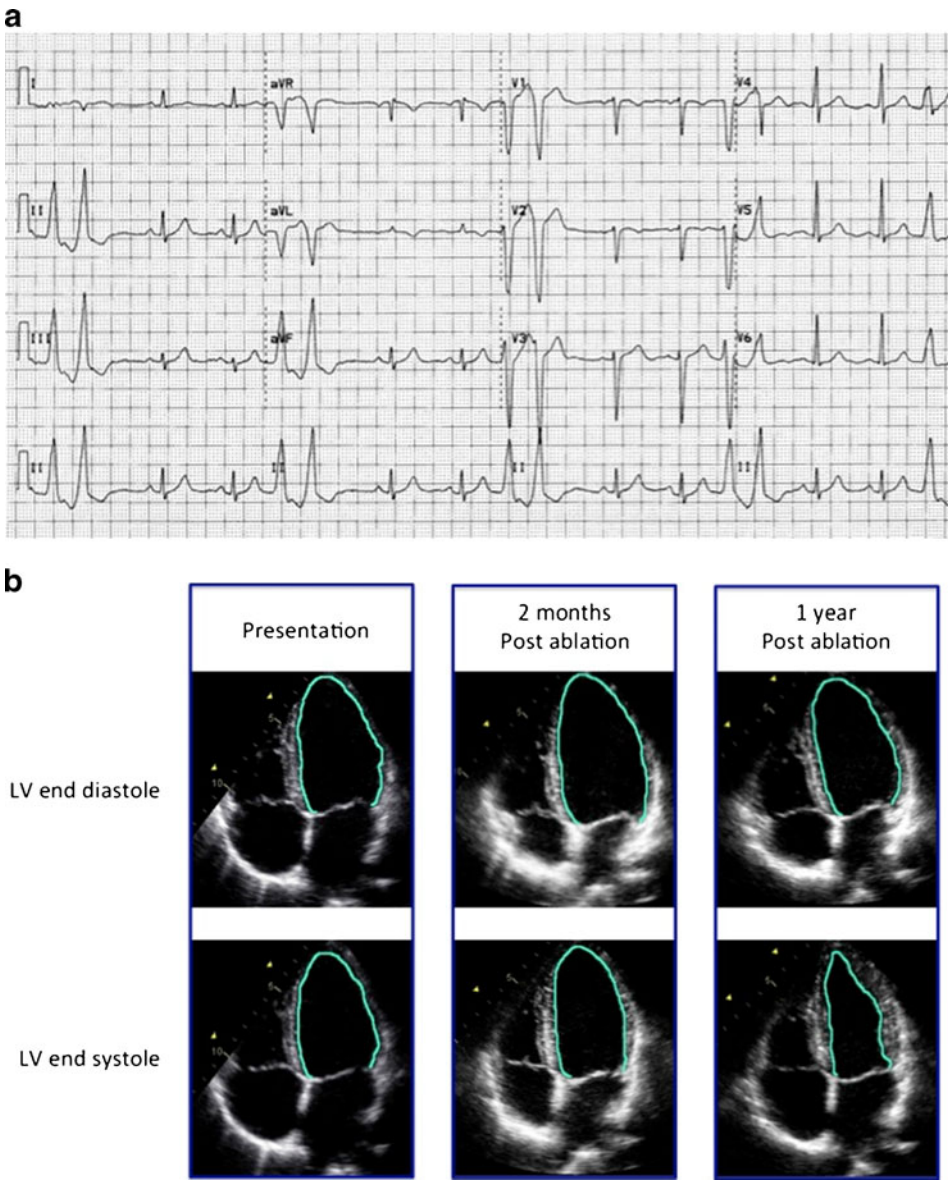

Fig. 1 Idiopathic ventricular tachycardia and tachycardia-induced cardiomyopathy. A 45-year-old healthy woman was incidentally noted to have frequent PVCs on routine ECG **a** performed by her PCP. Further questioning revealed fatigue and dyspnea on exertion. An echocardiogram **b** was performed, which revealed a dilated LV cavity and an LVEF of 20 %. A cardiac catheterization was normal. She was referred to our hospital with a diagnosis of idiopathic dilated cardiomyopathy for ICD implantation. Given concern for possible tachycardia-induced cardiomyopathy, ICD implantation was deferred and a Holter monitor was performed, which revealed>60,000 PVCs (47 % of total beats) and NSVT at 160 bpm up to 9 beats in length. An EP Electrohysiology study was performed, which localized her PVCs and NSVT to the RVOT. Following focal ablation, she had no further ventricular ectopy or NSVT. Her symptoms improved following ablation, and a repeat echocardiogram **b** performed 2 months post-ablation revealed a mildly dilated LV cavity with an improved LVEF to 45 %. A subsequent echocardiogram **b** 1 year after her ablation revealed normal LV cavity size and systolic function PVCs = premature ventricular contractions, ECG = electrocardiogram, PCP = primary care provider, LV = left ventricle, LVEF = left ventricular ejection fraction, ICD = implantable cardioverter defibrillator, NSVT = nonsustained ventricular tachycardia, RVOT = right ventricular outflow tract

PVCs in a 24-hour period. PVC burdens between 16 and 24 % have been reported in the literature as cutoffs that best separate patients with and without TIC [42, 77•, 79•]. However, these cutoff values often fail to identify every individual at risk of cardiomyopathy, and the critical burden for some patients can be lower. From the perspective of absolute PVC number, > 20,000 PVCs in 24 hours was reported to correlate with a reduction in LVEF [87•, 88]. Another study reported that dividing patients into groups based on total PVC burden from<1,000 PVCs/day, 1,000–10,000 PVCs/day, and>10,000 PVCs/day yielded a graded prevalence of LV dysfunction of 4 %, 12 %, and 34 %, respectively [89].

It is clear that the likelihood of TIC development increases with increasing PVC burden. However, what is also clear is

that PVC burden is not the only contributing factor to impaired LV function. PVC QRS duration has been associated with the likelihood of TIC development, with PVC QRS durations of≥140 msec and≥150 msec reported as predictive of impaired LVEF [84•, 87•]. PVC QRS duration has also been reported to independently predict reversibility of LV dysfunction, with a greater PVC duration predicting a lower likelihood of recovery [83•].

As with all forms of TIC, PVC-induced cardiomyopathy reverses with catheter ablation of PVCs in the majority of cases [79•, 90•]. It appears that complete elimination of PVCs is not necessary for improvement in LV function, and several studies have reportedly that an 80 % reduction in PVC burden is sufficient to allow for LVEF improvement in a majority of cases [82•, 85•], although the magnitude of LVEF improvement has been correlated with decline in residual PVC burden [82•]. These findings are important, given that total elimination of some idiopathic PVCs can be challenging due to origins difficult to ablate from a transvenous approach.

Diagnostic Approach and Treatment

TIC should be suspected when a patient presents with newly diagnosed LV dysfunction with or without heart failure symptoms and a persistent or frequently occurring tachycardia or frequent PVCs. However, patients with TIC may not present in their causative arrhythmia, and a high index of suspicion is necessary to appropriately identify patients. As noted above, the exact ventricular rate necessary for the development of TIC is unknown and with AF or PVCs; true tachycardia does not have to be present to induce LV dysfunction. Also important to recognize is that resting heart rates are poor indicators of overall heart rates, given the response of ventricular rates to physical activity, particularly with AF, atrial flutter, incessant AT, and PVCs. Evidence of previously normal LV systolic function can be an important clue, especially in the absence of intervening events such as myocardial infarction. However, TIC is not excluded by the presence of underlying structural heart disease, and can occur in association with other forms of heart disease. In this case, the presence of a persistent tachycardia can worsen already reduced systolic function. One clue may be that the degree of LV dysfunction is out of proportion to the severity of other comorbidities. In patients who carry a diagnosis of "idiopathic" dilated cardiomyopathy, consideration should be given to monitoring for subclinical arrhythmia with ambulatory monitors, given the potential for reversal of LV dysfunction if a persistent tachycardia is discovered. Such a finding may significantly alter a patient's treatment strategy (Fig. 1).

Noninvasive imaging techniques have minimal utility in differentiating TIC from other forms of cardiomyopathy. One study reported that patients with TIC and no other underlying structural disease have a smaller LV end-diastolic diameter, LV volume when adjusted for body surface area, and LV mass index as compared to patients with idiopathic dilated cardiomyopathy at the time of initial presentation. In this study, LV end-diastolic dimension was the only independent predictor of TIC in multiple regression analysis, and was felt to be the best echocardiographic predictor of TIC [91]. In clinical practice, this finding may raise suspicion of TIC in the appropriate setting, but would not be enough to confirm a diagnosis. Once the diagnosis of TIC is suspected, an aggressive strategy of rate or rhythm control should be pursued, with close monitoring of heart failure symptoms and LV function, to determine if improvement in heart failure and cardiomyopathy follows.

Timing of Recovery

There have been fewer reports in the literature regarding the time course of recovery in humans with TIC. An early study of patients with atrial fibrillation and LV dysfunction who were treated with cardioversion reported no change in ejection fraction 24 hours or 1 week after cardioversion. However, 1 month after cardioversion, the ejection fraction had improved to close to normal, and remained stable at 6 months of follow-up [51]. A case report of a patient with incessant atrial tachycardia treated with ablation revealed similar results. Ten days following ablation, no change was seen in the patient's ejection fraction. However, at 1 month, a significant improvement was demonstrated, and LV function had normalized by 3 months of follow-up [92]. Another study of AV junction ablation for atrial fibrillation reported that LV function significantly improves at 1-month and 6-month follow-up, although earlier follow-up was not performed in this study [93].

The timing of recovery has also been reported after ablation of PVCs in patients with TIC. One study reported that LV function normalized in more than 80 % of patients after a mean of 3 months following catheter ablation. A small subset of these patients had echocardiograms performed 1 week following ablation, with 80 % showing improved LV function [79•]. A more recent study found that the majority of patients had recovery in LV function within 4 months, but in 32 % of patients, recovery took longer than 4 months and up to 45 months in some patients [85•]. The most recent study of PVC-induced cardiomyopathy 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 [90•].

The delay in recovery of LV function may be related to the negative remodeling that has been associated with TIC in animal models. One study examined echocardiographic changes in patients with TIC after resolution of their respective tachycardias. The mean time interval between pre-treatment and post-treatment echocardiograms was 14 months. In these patients, although the majority of echocardiographic abnormalities

normalized, including ejection fraction, following control of the causative tachycardia, patients with TIC had a significantly higher stroke volume, cardiac index, LV end-systolic dimension, LV end-systolic volume index, and LV end-diastolic index when compared to gender, age, and ejection fraction matched controls [94].

Risk of Recurrence

It has been reported that recurrent tachycardia in patients with a prior history of TIC can lead to recurrent cardiomyopathy at a faster and more severe rate compared to initial presentations, suggesting that although LVEF normalizes, structural abnormalities persist. In a cohort of 24 patients with TIC, five patients were noted to have recurrent tachycardia. In all five patients, an abrupt drop in ejection fraction was noted and all patients developed clinical heart failure within 6 months. Heart failure was reversed over a similar 6-month period once adequate rate control was established [95]. A separate case series also reported recurrence in two of twelve consecutive patients during an average follow-up period of 53 months. In both patients, the time from tachycardia symptom onset to the development of recurrent heart failure was less than 2 weeks, and in one patient, it was in a single day. Both patients had a decline in LVEF to a level similar to their initial presentation. After control of the arrhythmias, both patients again normalized their ejection fractions [96]. An early study of TIC reported a severe deterioration in LV systolic function in two of twelve patients after reversion to AF following cardioversion [97]. The longest period of follow-up reported to date is from a single case report of a patient with TIC due to incessant atrial tachycardia that was successfully ablated. Following ablation, LVEF and LV chamber dimensions gradually improved and plateaued 1-year post ablation. After 7 years of stability in his LV function, the patient was reassured of his clinical status and his heart failure regimen was discontinued. He returned for follow-up 1 year later during which time he had remained asymptomatic. A repeat echocardiogram revealed depressed LV function. His medication regimen was reinitiated with subsequent improvement in his LV function [98].

Reports of precipitous decline in LV function following tachycardia recurrence and late recurrence of LV function after discontinuation of medications would suggest persistent structural abnormalities in patients with TIC. This is also supported by evidence of negative remodeling seen in the echo cardiography study previously described. These findings highlight the importance of maintaining a strong medical heart failure regimen for patients with TIC, even after normalization of their ejection fraction; furthermore, routine monitoring for arrhythmia recurrence should be considered.

Risk of Sudden Death

There is little published data on the risk of sudden death in the setting of TIC. Heart failure is known to cause an arrhythmogenic substrate, with repolarization abnormalities being most commonly implicated in the genesis of ventricular arrhythmias in heart failure. Animal models of TIC have reported conflicting results regarding the risk of ventricular arrhythmias. Prolonged repolarization has been reported in a porcine model of TIC, but no deaths due to polymorphic VT were reported in these animals [99]. However, a canine model of TIC also reported repolarization abnormalities, and some of these animals did develop polymorphic VT, the incidence of which increased as heart failure progressed [100]. In the setting of clinical heart failure and depressed ejection fraction, one would suspect an increased risk of malignant arrhythmias. However, the question remains whether patients with resolved TIC and normal LV function continue to have an increased risk of sudden death due to pathologic remodeling, which may or may not be apparent clinically. Case reports of patients with TIC who have died suddenly have been published in the literature. One center reported three patients with a history of TIC who died suddenly. All three patients had TIC in the setting of atrial fibrillation and all patients' LVEF normalized or near normalized with various treatment strategies including cardioversion, antiarrhythmic drugs (AADs), and an ablate and pace strategy. All patients died months to years after normalization of their ejection fraction and per reports, had no heart failure symptoms nor symptoms of recurrent arrhythmia prior to death. Of note, these three patients had significantly lower baseline LVEFs compared to other patients with TIC [95]. A second study reported a patient with atrial flutter and cardiomyopathy that recovered with heart rate control after 8 months of therapy. The patient died suddenly 4 years after his initial presentation, without preceding symptoms of tachycardia or CHF. At the time of this patient's initial presentation with heart failure, he had the highest levels of BNP b-type natriuretic peptide of all patients with TIC reported, although the significance of this is unclear [96].

Conclusion

TIC is a complex disorder encompassing a wide range of causative arrhythmias, clinical presentations, and natural histories. Our current understanding of the mechanisms of LV dysfunction is limited, despite extensive work with animal models, as the applicability to human disease has yet to be proven. The diagnosis of TIC remains challenging, and a high index of suspicion is required, given the potential for LV recovery with appropriate treatment. An aggressive approach to arrhythmia treatment, whether it be catheter ablation, AADs, or rate control, is important in patients with otherwise

idiopathic cardiomyopathy when TIC is suspected. Further study of the risk factors for development of TIC will be an important area of future research to help better identify patients likely to develop cardiomyopathy in the setting of tachycardia. This may also help identify patients who are likely to have improvement in their cardiomyopathy with appropriate treatment of their arrhythmia. Ongoing medical management of cardiomyopathy despite resolution of LV function appears to be important, although further study is necessary. Future areas of research including pathophysiology in humans, genetic polymorphisms, and novel imaging approaches may further aid the clinical evaluation and treatment of these complex patients.

Compliance with Ethics Guidelines

Conflict of Interest Ethan R. Ellis declares that he has no conflict of interest.

Mark E. Josephson declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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