Diagnosis and Management of Tachycardia-Induced Cardiomyopathy

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Korean Heart Rhythm Society

COI Disclosure

Young Kuk Cho:

The author have no financial conflicts of interest to disclose concerning the presentation

Overview

Tachycardia-Induced Cardiomyopathy (TIC)

- Definition
- Epidemiology
- Pathophysiology
- Tachycardia associated TIC
- Signs and symptoms
- ECG findings
- Diagnostic testing
- Treatment
- Follow-up
- Prognosis

Introduction

Tachycardia-Induced Cardiomyopathy (TIC)

= Tachycardiomyopathies
important cause of LV dysfunction
should be recognised by physicians
potentially reversible

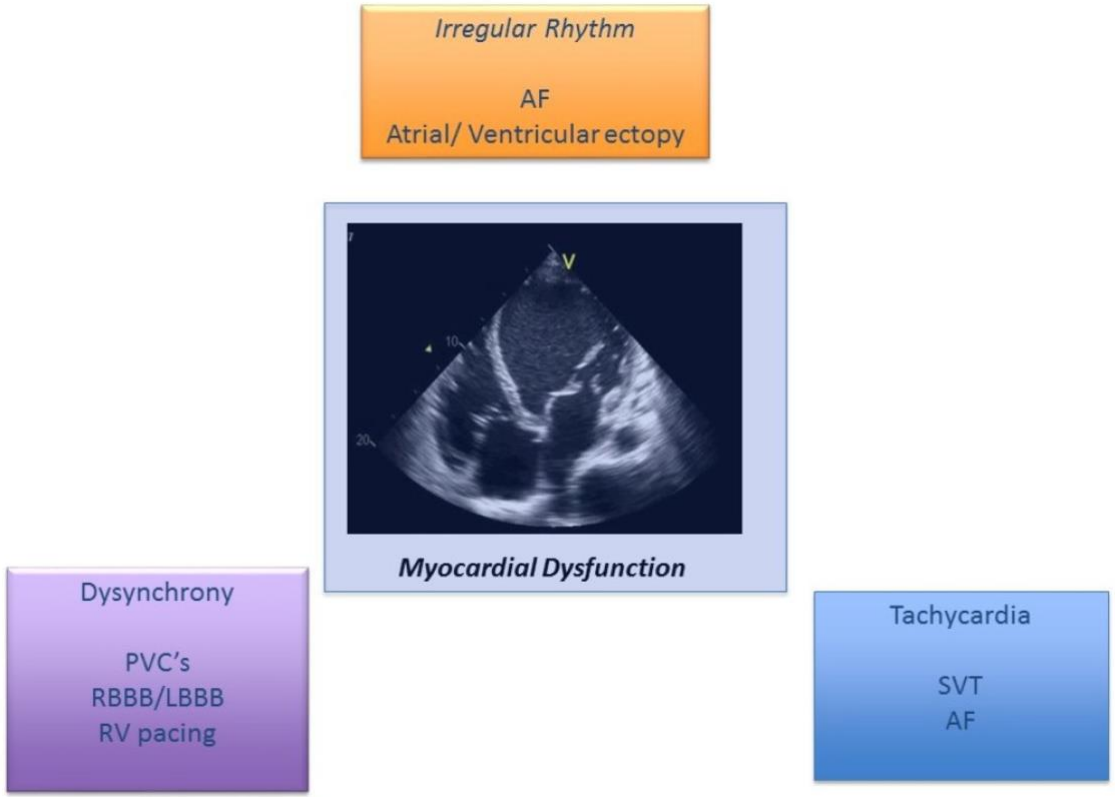
Definition - classically

as the reversible impairment of ventricular function
induced by persistent arrhythmia
TIC can be induced by atrial & ventricular ectopy promoting dyssynchrony
→ ‘arrhythmia-induced cardiomyopathy ’

Introduction

Proposed definition

'Atrial and/or ventricular dysfunction secondary to rapid and/or asynchronous/irregular myocardial contraction, partially or completely reversed after treatment of the causative arrhythmia'



Introduction

Proposed definition

‘Atrial and/or ventricular dysfunction
secondary to rapid and/or asynchronous/irregular myocardial contraction,
partially or completely reversed after treatment of the causative arrhythmia’

Two categories

Arrhythmia-induced

arrhythmia is the only reason for ventricular dysfunction

Arrhythmia-mediated

arrhythmia exacerbates ventricular dysfunction
and/or worsens heart failure (HF) in concomitant heart disease

EPIDEMIOLOGY

exact incidence of Tachycardia-induced cardiomyopathy (TIC)
remains unclear

Some insight into the prevalence of TIC can be derived
from cohort studies

- cohort of 331 pt.: referred for catheter ablation of incessant AT,
  myocardial dysfunction : 9%
  TIC were younger (39 vs 51 yr)
  frequently male (60 vs 38 %)
  incessant or very frequent paroxysmal tachycardia (100 vs 20%)

J Am Coll Cardiol 2009; 53:1791.

- cohort of 625 - catheter ablation for a variety of tachyarrhythmias
  TIC : 2.7 %

J Interv Card Electrophysiol 2013;36:27.

- cohort of 1269 - catheter ablation for atrial flutter
  184 pt. (14.5%) : reduced LVEF (<40 %)

Eur J Heart Fail 2016; 18:394.

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Heart Rhythm Disorders

Tachycardia-Mediated Cardiomyopathy Secondary to Focal Atrial Tachycardia

Long-Term Outcome After Catheter Ablation

Caroline Medi, BMED,*† Jonathan M. Kalman, MBBS, PHD,* Haris Haqqani, MBBS,* Jitendra K. Vohra, MD,* Joseph B. Morton, MBBS, PHD,* Paul B. Sparks, MBBS, PHD,* Peter M. Kistler, MBBS, PHD*‡

Melbourne, Australia

Objectives This study aimed to characterize the incidence, clinical and electrophysiologic features, and long-term outcomes of patients with tachycardia-mediated cardiomyopathy (TCM) secondary to focal atrial tachycardia (AT).

Background TCM is known to complicate atrial tachyarrhythmias. Little is known of the patient and tachycardia characteristics associated with the development of left ventricular (LV) dysfunction and the long-term outcomes after cure of tachycardia.

Methods A total of 345 patients with focal AT underwent radiofrequency ablation between January 1997 and July 2008. A retrospective analysis was performed to identify patients with LV dysfunction, defined as an ejection fraction <50% on echocardiography. Patients with pre-existing structural heart disease (n = 14) were excluded. Patients with TCM (n = 30) and without TCM (n = 301) were compared. Recovery of LV function was also assessed.

Results The incidence of TCM was 10%. Incessant or very frequent paroxysmal tachycardia was strongly associated with TCM, compared to patients without TCM (100% vs. 20%, $p < 0.001$). Patients in the TCM group were younger (mean age 39 ± 22 years vs. 51 ± 17 years, $p = 0.0006$) and more frequently male (60% vs. 38%, $p < 0.001$). Patients with TCM had a longer mean tachycardia cycle length (502 ± 131 ms vs. 402 ± 105 ms, $p < 0.0001$) and slower ventricular rate (117 ± 21 beats/min vs. 141 ± 33 beats/min, $p = 0.0007$) during tachycardia compared with patients who did not have TCM. Appendage sites are associated with a high incidence of incessant tachycardia (84%) and LV dysfunction (42%). After successful ablation, LV function was restored in 97% of patients at a mean of 3 months.

Conclusions Cardiomyopathy occurs in 10% of patients with focal AT. A slower incessant tachycardia is more frequently complicated by cardiomyopathy. Long-term restoration of LV function can be achieved after successful catheter ablation of the tachycardia focus. (J Am Coll Cardiol 2009;53:1791–7) © 2009 by the American College of Cardiology Foundation

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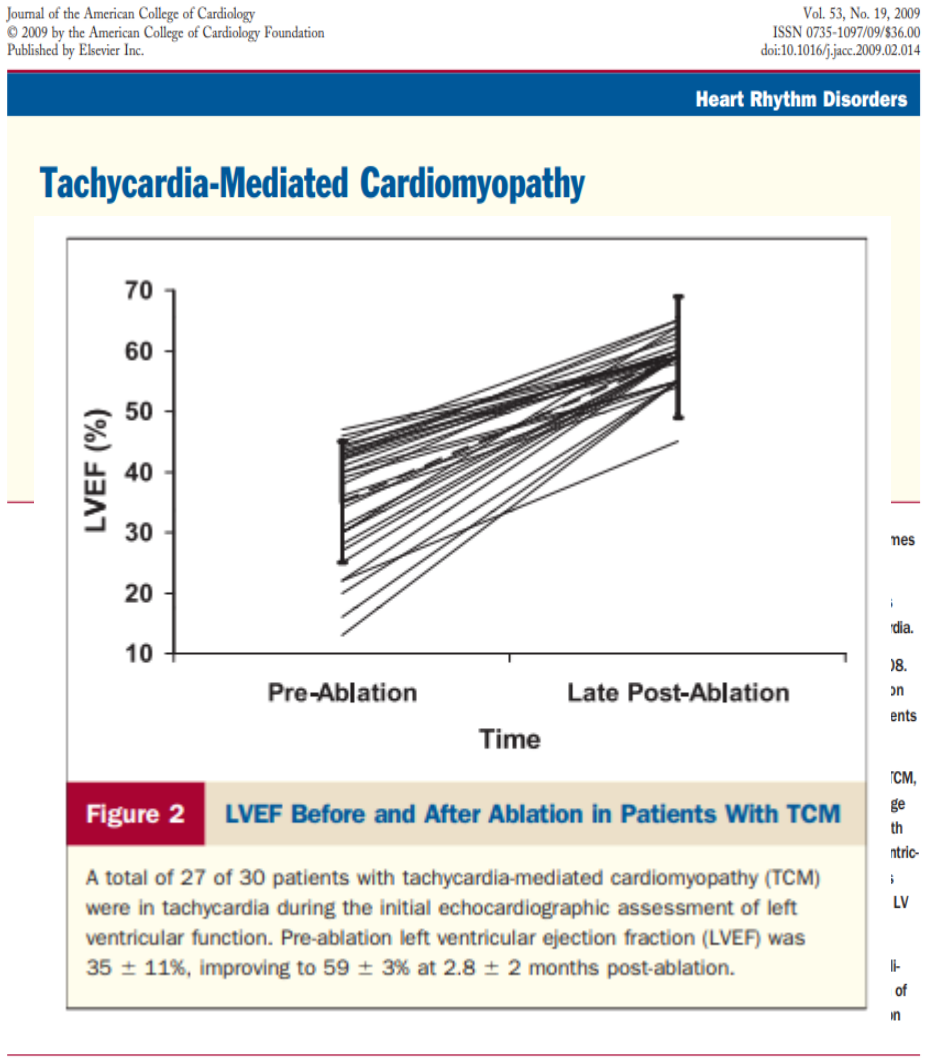

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J Interv Card Electrophysiol. 2013 Jan;36(1):27-32; discussion 32. doi: 10.1007/s10840-012-9727-9. Epub 2012 Oct 23.

Reversal of cardiomyopathy in patients with congestive heart failure secondary to tachycardia

Zhao Donghua [1], Peng Jian, Xiao Zhongbo, Zhang Feifei, Peng Xinhui, Yang Hao, Liu Fuqiang, Li Yan, Xie Yong, Huang Xinfu, Meng Surong, Wu Muli, Xu Dingli

Affiliations + expand

PMID: 23090777 DOI: 10.1007/s10840-012-9727-9

Abstract

Objectives: Tachycardia-induced cardiomyopathy (TCM) is a reversible cause of heart failure. Little is known of the characteristics of tachycardia associated with the development of left ventricular (LV) dysfunction and the reversal of cardiomyopathy after cure of tachycardia. This study aimed to examine the reversal of cardiomyopathy in patients undergoing ablation with congestive heart failure secondary to tachycardia.

Methods: A total of 625 patients underwent radiofrequency ablation for tachycardiarrhymias between January 2009 and July 2011. Echocardiography analysis was performed to identify patients with depressed LV function, defined as a left ventricular ejection fraction <50 %. Patients with preexisting structural heart disease (n = 10) were excluded. NT-pro-B-type natriuretic peptide (NT-proBNP) assessment was performed before ablation in patients considered to have TCM (n = 17). Repeated echocardiography study and NT-proBNP assessment were measured after a mean follow-up of 3 months. Levels of NT-proBNP before and after ablation were compared. Reversal of cardiomyopathy was also assessed.

Results: The incidence of TCM was 2.7 % (12 males; age, 35.8 ± 17.1 years). Successful ablation was performed in 16 of 17 patients (94.1 %). There was a significant improvement in left ventricular ejection fraction (36.7 ± 7.5 vs. 59.4 ± 9.7 %; P < 0.001). The mean left ventricular end-diastolic diameter before treatment was 59.5 ± 8.3 mm (range, 43 to 70), compared with 51.9 ± 7.4 mm (range, 40 to 67) (P = 0.009) after 3 months follow-up. The levels of NT-proBNP decreased after ablation procedure, from 4,092.6 ± 3,916.6 to 478.9 ± 881.9 pg/ml (P < 0.001). After successful ablation, ventricular function normalized in 15 of 17 (88.2 %) patients at a mean of 3 months.

Conclusions: Restoration of LV function and reversal of LV remodeling can be achieved with successful elimination of tachycardia in the majority of patients. NT-proBNP level elevates in subjects with TCM and decreases sharply after ablation.

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European Journal of Heart Failure (2016) 18, 394–401
doi:10.1002/ejhf.482

RESEARCH ARTICLE

Predictors and prognostic significance of tachycardiomyopathy: insights from a cohort of 1269 patients undergoing atrial flutter ablation

Béatrice Brembilla-Perrot[1]*, João Pedro Ferreira[2,3], Vladimir Manenti[1], Jean Marc Sellal[1], Arnaud Olivier[1], Thibaut Villemin[1], Daniel Beurrier[1], Christian De Chillou[1], Pierre Louis[1], Alice Brembilla[4], Yves Juillière[1], and Nicolas Girerd[2]

[1]Department of Cardiology Nancy University Hospital, Rue du Morvan 54511, Vandoeuvre-les-Nancy, France; [2]INSERM, Centre d'Investigations Cliniques Plurithématique 1433, Université de Lorraine, CHRU de Nancy and F-CRIN INI-CRCT, Nancy, France; [3]Department of Physiology and Cardiothoracic Surgery, Cardiovascular Research and Development Unit, Faculty of Medicine, University of Porto, Porto, Portugal; and [4]Epidemiology Department, CHU de Besançon, France

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Background Atrial flutter-related tachycardiomyopathy (AFL-TCM) is a rare and treatable cause of heart failure. Little is known about its epidemiology and long-term prognosis. Our aims are to determine the prevalence, predictors and outcomes of AFL-TCM.

Methods and results A total of 1269 patients were referred for radiofrequency ablation of AFL between January 1996 and September 2014; 184 had reduced left ventricular ejection fraction (LVEF <40%). At 6 months after AFL ablation, 103 patients (8.1% of the population, 56% of patients with baseline LVEF <40%) had marked LVEF improvement: these were considered to have AFL-TCM. Patients with persisting reduced LVEF were considered to have systolic dysfunction unrelated to AFL. Patients were followed for a median (percentile$_{25-75}$) of 1.15 (0.4–2.8) years. Patients with AFL-TCM were younger, had lower prevalence of ischaemic cardiomyopathy and used less antiarrhythmic drugs than patients with systolic dysfunction unrelated to AFL. In multivariable analysis, ischemic cardiomyopathy [odds ratio (OR) = 0.32, 95% confidence interval (CI) 0.15–0.68) $P = 0.003$] and prescription of antiarrhythmic drug before ablation [OR = 0.41, 95% CI 0.20–0.84, $P = 0.02$] were significantly associated with a lower probability of LVEF improvement during follow-up. Patients with AFL-TCM had similar survival to patients without systolic dysfunction at baseline [hazard ratio (HR) = 0.96 95% CI 0.34–2.65, $P = 0.929$], whereas patients with systolic dysfunction unrelated to AFL had higher mortality rates compared with patients without systolic dysfunction at baseline [HR = 2.88, 95% CI 1.45–5.72, $P = 0.002$].

Conclusions Marked LVEF improvement was observed in 56% of patients with baseline LVEF <40% at 6 months after ablation. These patients had similar survival to patients without baseline systolic dysfunction, whereas patients who remained with LVEF <40% had a threefold increase in mortality rates.

Keywords Tachycardiomyopathy • Atrial flutter • Ablation • Outcomes

PATHOPHYSIOLOGY

Chronic tachycardia → produces significant cardiac structural changes,
including LV dilation and cellular morphologic changes
exact mechanism by which tachycardia produces these changes
not well defined.

Am J Physiol 1990; 259:H218.

Animal models : developed in the investigation of heart failure (HF)
studied extensively in the evaluation of TIC

- Rapid pacing →
  marked depression of LVEF, elevated filling pressures,
  depressed cardiac output, increased systemic vascular resistance
- generally reversible with cessation of the tachycardia,
  although in some cases LVEF may not return

J Am Coll Cardiol 1989; 14:489.

Can J Physiol Pharmacol 1988; 66:1505.

Depletion of myocardial energy stores and myocardial ischemia

in animal models :
persistent tachycardia →

- depletes high-energy stores
  by reduced myocardial levels of creatine, phosphocreatine,
  & adenosine triphosphate (ATP),
  diminished activity of the Na-K-ATPase pump — Am J Physiol 1995; 268:H836.
- probably due to alterations in cellular metabolism
  with mitochondrial injury — Can J Physiol Pharmacol 1990; 68:34.
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Myocardial ischemia
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: seen in ischemic models following vessel occlusion
High-energy stores return to normal within days

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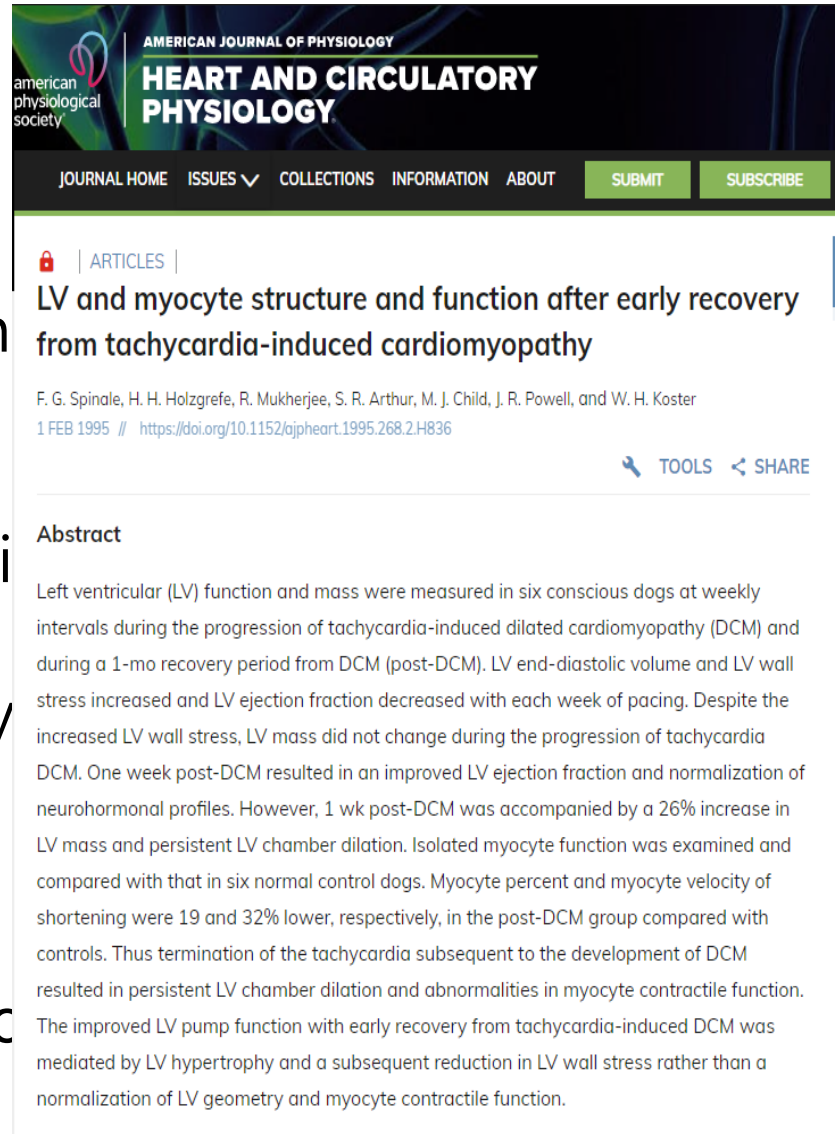

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ARTICLES

Chronic supraventricular tachycardia causes ventricular dysfunction and subendocardial injury in swine

F. G. Spinale, D. A. Hendrick, F. A. Crawford, A. C. Smith, Y. Hamada, and B. A. Carabello

01 JUL 1990 // https://doi.org/10.1152/ajpheart.1990.259.1.H218

PDF (6 MB) TOOLS SHARE

Abstract

Chronic supraventricular tachycardia has been associated with ventricular dysfunction in humans and animals. However, this ventricular failure is poorly characterized, and the ultrastructural consequences of supraventricular tachycardia are unknown. We serially examined right and left ventricular function, endomyocardial ultrastructure, and creatine kinase activity in eight pigs at base line and again at 1, 2, and 3 wk following rapid atrial pacing. Left and right ventricular ejection fractions fell significantly from base line after 1 wk of chronic tachycardia. Three weeks of chronic pacing resulted in further deterioration in ejection fractions. Significant biventricular chamber dilatation developed and was associated with a reduction in end-diastolic wall thickness after 2 wk of tachycardia. Mitochondrial injury and diminished mitochondrial cytochrome oxidase staining of subendocardial myocytes were observed after 2 wk of tachycardia. Endomyocardial creatine kinase activity fell from control levels following 2 wk of pacing. Postmortem examination revealed a reduction in left ventricular wall thickness compared with 14 control animals. Fibrosis occurred along the subendocardial layer in paced animals, and glycogen content was also reduced. In summary, chronic

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Abnormal calcium handling and beta adrenergic responsiveness

Abnormalities in both calcium channel activity
& sarcoplasmic reticulum calcium transport
contribute to the myocardial dysfunction in TIC

Can J Physiol Pharmacol 1990; 68:34.

Diminished beta-adrenergic responsiveness
has also been described and may be due to reduced
Myocyte beta-1 receptor density (down regulation)

Eur Heart J 1992; 13 Suppl E:47.

Circ Res 1991; 69:1546.

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Abnormalities in Intracellular Calcium Regulation and Contractile Function in Myocardium from Dogs with Pacing-induced Heart Failure

Cynthia L. Perreault, Richard P. Shannon, Kazuo Komamura, Stephen F. Vatner, and James P. Morgan
Charles A. Dana Research Institute and the Harvard-Thorndike Laboratory of Beth Israel Hospital, Department of Medicine (Cardiovascular Division), Harvard Medical School, Boston, Massachusetts 02215; and the New England Regional Primate Research Center, Southborough, Massachusetts 01772

Abstract

24 d of rapid ventricular pacing induced dilated cardiomyopathy with both systolic and diastolic dysfunction in conscious, chronically instrumented dogs. We studied mechanical properties and intracellular calcium (Ca_i^{2+}) transients of trabeculae carneae isolated from 15 control dogs (n = 32) and 11 dogs with pacing–induced cardiac failure (n = 26). Muscles were stretched to maximum length at 30°C and stimulated at 0.33 Hz; a subset (n = 17 control, n = 17 myopathic) was loaded with the $[Ca^{2+}]_i$ indicator aequorin. Peak tension was depressed in the myopathic muscles, even in the presence of maximally effective (i.e., 16 mM) $[Ca^{2+}]$ in the perfusate. However, peak $[Ca^{2+}]_i$ was similar (0.80±0.13 vs. 0.71±0.05 μM; $[Ca^{2+}]_o$ = 2.5 mM), suggesting that a decrease in Ca_i^{2+} availability was not responsible for the decreased contractility. The time for decline from the peak of the Ca_i^{2+} transient was prolonged in the myopathic group, which correlated with prolongation of isometric contraction and relaxation. However, similar end-diastolic $[Ca^{2+}]_i$ was achieved in both groups (0.29±0.05 vs. 0.31±0.02 μM), indicating that Ca_i^{2+} homeostasis can be maintained in myopathic hearts. The inotropic response of the myopathic muscles to milrinone was depressed compared with the controls. However, when cAMP production was stimulated by pretreatment with forskolin, the response of the myopathic muscles to milrinone was improved. Our findings provide direct evidence that abnormal $[Ca^{2+}]_i$ handling is an important cause of contractile dysfunction in dogs with pacing-induced heart failure and suggest that deficient production of cAMP may be an important cause of these changes in excitation-contraction coupling. (*J. Clin. Invest.* 1992. 89:932–938.) Key words: aequorin • cardiomyopathic dogs • intracellular calcium handling • pacing-induced cardiac failure

malities in intracellular calcium $(Ca_i^{2+})^i$ handling as a major factor contributing to both systolic and diastolic dysfunction (for review, see reference 1). Although many animal models of pressure-overload hypertrophy and myocardial failure have been studied, none have documented the same pathophysiological changes as observed in human myocardium. A finding unique to myopathic human myocardium is that the Ca_i^{2+} transient recorded with aequorin or Indo-1 is, under some circumstances, composed of two distinct components that appear to reflect both sarcoplasmic reticular and sarcolemmal dysfunction (2, 3). Studies in several small animal models of cardiac hypertrophy and failure, including the spontaneously hypertensive rat, pulmonary-artery banded ferret, and congenitally myopathic Syrian hamster, have demonstrated prolonged Ca_i^{2+} transients, but none have yet reproduced the two distinct components (1). In addition, myopathic human myocardium appears to have a unique pharmacological profile suggestive of deficient intracellular production of cAMP, which, in turn, appears to diminish the effectiveness of cAMP-dependent inotropic agents (4).

The purpose of the present study was to investigate myocardial function and Ca_i^{2+} handling in a large animal model of heart failure, which may more closely resemble cardiac failure in humans than do previous studies of small animal models of cardiac hypertrophy and/or failure (5, 6). A major advantage of this model is the availability of both in vivo and in vitro measures of contractile function, which permits correlation between hemodynamic manifestations of heart failure and cellular alterations in excitation–contraction coupling.

Methods

Dilated cardiomyopathy was induced in conscious, chronically instru-

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Abnormalities in Intracellular Calcium Regulation and Contractile Function in Myocardium from Dogs with Pacing-induced Heart Failure

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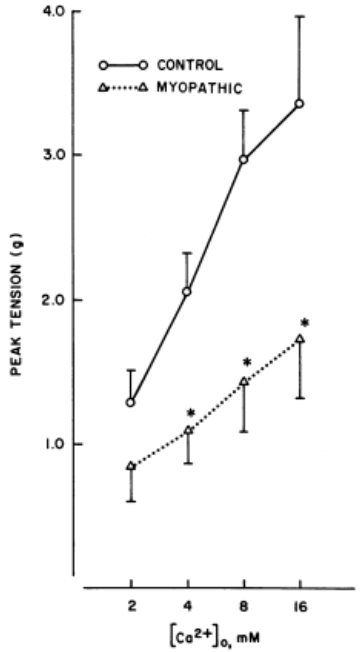

Figure 2. Concentration-response curve to $[Ca^{2+}]_o$ in muscles from sham-operated control (○) and cardiomyopathic (△) dogs. The peak isometric tension developed at 3-s intervals of stimulation is plotted on the ordinate and the millimolar Ca^{2+} concentration in the perfusate is plotted on the abscissa. Values are means±SEM; * $P < 0.05$ vs. control.

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Oxidative stress and injury

In patients with AF and atrial dysfunction
histologic evidence of oxidative stress
& injury in the atrial myocardium

Circulation 2001; 104:174.

This results in peroxynitrite formation
modifies myofibrillar proteins,
contributes to loss of fibrillar protein function,
& alters myofibrillar energetics.

Role of oxidative stress from one animal study
administration of the antioxidant vitamins E, C, & beta-carotene
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Circulation
Volume 104, Issue 2, 10 July 2001; Pages 174-180
https://doi.org/10.1161/01.CIR.104.2.174

CLINICAL INVESTIGATION AND REPORTS

Impaired Myofibrillar Energetics and Oxidative Injury During Human Atrial Fibrillation

Michael J. Mihm, PhD, Fushun Yu, PhD, Cynthia A. Carnes, PharmD, PhD, Peter J. Reiser, PhD, Patrick M. McCarthy, MD, David R. Van Wagoner, PhD, and John Anthony Bauer, PhD

ABSTRACT: ***Background—*** Atrial fibrillation (AF) is associated with severe contractile dysfunction and structural and electrophysiological remodeling. Mechanisms responsible for impaired contractility are undefined, and current therapies do not address this dysfunction. We have found that myofibrillar creatine kinase (MM-CK), an important controller of myocyte contractility, is highly sensitive to oxidative injury, and we hypothesized that increased oxidative stress and energetic impairment during AF could contribute to contractile dysfunction.***Methods and Results—*** Right atrial appendages were obtained from AF patients undergoing the Maze procedure and from control patients who were in normal sinus rhythm and undergoing cardiac surgery. MM-CK activity was reduced in AF patients compared with controls (25.4±3.4 versus 18.2±3.8 μmol/mg of myofibrillar protein per minute; control versus AF; $P<0.05$). No reduction in total CK activity or myosin ATPase activity was detected. This selective reduction in MM-CK activity was associated with increased relative expression of the β-myosin isoform (25±6 versus 63±5%β, CTRL versus AF; $P<0.05$). Western blotting of AF myofibrillar isolates demonstrated no changes in protein composition but showed increased prevalence of protein oxidation as detected by Western blotting for 3-nitrotyrosine (peroxynitrite biomarker) and protein carbonyls (hydroxyl radical biomarker; $P<0.05$). Patterns of these oxidative markers were distinct, which suggests discrete chemical events and differential protein vulnerabilities in vivo. MM-CK inhibition was statistically correlated to extent of nitration ($P<0.01$) but not to carbonyl presence.***Conclusions—*** The present results provide novel evidence of oxidative damage in human AF that altered myofibrillar energetics may contribute to atrial contractile dysfunction and that protein nitration may be an important participant in this

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Circulation
Volume 104, Issue 2, 10 July 2001; Pages 174-180
https://doi.org/10.1161/01.CIR.104.2.174

CLINICAL INVESTIGATION AND REPORTS

Impaired Myofibrillar Energetics and Oxidative Injury During Human Atrial Fibrillation

Michael J. Mihm, PhD, Fushun Yu, PhD, Cynthia A. Carnes, PharmD, PhD, Peter J. Reiser, PhD, Patrick M. McCarthy, MD, David R. Van Wagoner, PhD, and John Anthony Bauer, PhD

ABSTRA
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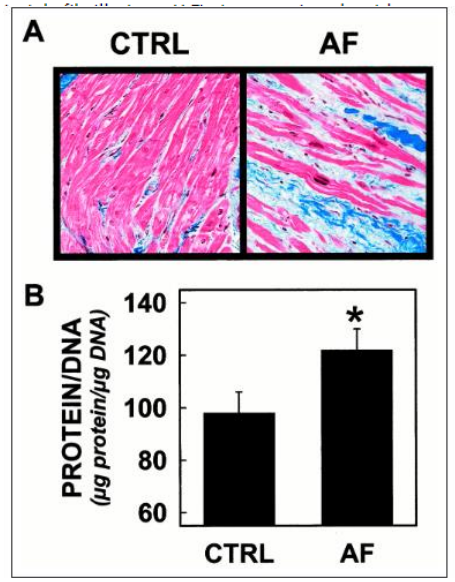

Figure 1. Atrial myocyte hypertrophy and fibrosis deposition was observed during AF. A, Trichrome-stained AF and control right atrial appendages (×400). AF atria demonstrated interstitial fibrosis (blue staining), myocyte elongation, and hypertrophy. B, Protein/DNA ratios were increased in AF atria. CTRL indicates control (normal sinus rhythm). *P<0.05.

contractile dysfunction and that protein nitration may be an important participant in this

Oxidative stress and injury

In patients with AF and atrial dysfunction
histologic evidence of oxidative stress
& injury in the atrial myocardium

Circulation 2001; 104:174.

This results in peroxynitrite formation
modifies myofibrillar proteins,
contributes to loss of fibrillar protein function,
& alters myofibrillar energetics.

Role of oxidative stress from one animal study
administration of the antioxidant vitamins E, C, & beta-carotene
→ attenuated the cardiac dysfunction
& prevented beta receptor downregulation

J Am Coll Cardiol 2001; 38:1734.

Genetic basis and ACE gene polymorphism

An association has been reported
between a gene polymorphism & TIC

Int J Mol Med 2004; 13:455.

Levels of angiotensin converting enzyme (ACE)
associated with a 287 base pair insertion (I)/deletion (D)
polymorphism in intron 16 of the ACE gene
DD genotype is associated with
increased serum ACE levels
& a higher incidence of both ischemic & idiopathic DCMP

In a study comparing
20 patients with TIC,
20 controls with persistent tachycardia but normal LV function,
24 normal volunteers,
: DD genotype was significantly more common in TIC

Genetic basis and ACE gene polymorphism

An association has been reported
between a gene polymorphism & TIC
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associated with a 287 base pair
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DD genotype is associated with
increased serum ACE levels
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Association of angiotensin converting enzyme gene polymorphism with tachycardia cardiomyopathy

Authors: Pramod M. Deshmukh, Rajan Krishnamani, Mary Romanyshyn, Andrew K. Johnson, John D. Noti

View Affiliations

Published online on: March 1, 2004 https://doi.org/10.3892/ijmm.13.3.455

Pages: 455-458

Abstract

Despite incessant tachycardia, not all patients develop tachycardia-mediated cardiomyopathy. The cardiac renin-angiotensin system may be involved in cardiac remodelling and fibrosis. The level of angiotension-converting enzyme (ACE) in the serum is associated with a 287 bp insertion (I)/deletion (D) polymorphism in intron 16 of the ACE gene. The DD genotype is associated with increased serum ACE levels and a higher incidence of idiopathic dilated and ischemic cardiomyopathy. The objective of this study was to assess whether the ACE gene I/D polymorphism is responsible for development of tachycardia-mediated cardiomyopathy. We identified 20 consecutive patients with persistent tachycardia and cardiomyopathy who showed significant improvement in ejection fraction after rate control (group A, tachycardia cardiomyopathy group). We compared the I/D genotype frequency of group A with the gene frequency of a separate group of 20 patents who, despite rapid atrial arrhythmias had preserved left ventricular ejection fraction (group B, tachycardia without cardiomyopathy group). These two groups were then compared with 24 healthy normal volunteers (group C). After a mean follow-up of 30 months, group A patients showed

Histopathologic and immunologic findings

cohort of 189 patients with new onset HF and reduced LVEF
not related to valvular or ischemic heart disease
19 pt met criteria for TIC

J Am Coll Cardiol 2017; 70:1687.

- Endomyocardial biopsies in TIC
  compared with patients with idiopathic DCMP
  stronger myocardial expression of MCH class II molecule
  & enhanced infiltration of CD68+ macrophages
- TIC had fewer T cells and macrophages.
  compared to patients with ischemic cardiomyopathy
- Fibrosis was also less prominent in TIC
  However, electron microscopy
  showed abnormal mitochondrial distribution & enhanced myocyte size.

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Histopathological and Immunological Characteristics of Tachycardia-Induced Cardiomyopathy

Karin A.L. Mueller, MD,[a] David Heinzmann, MD,[a] Karin Klingel, MD,[b] Petra Fallier-Becker, PhD,[b] Reinhard Kandolf, MD,[b] Antonios Kilias, MD,[a] Britta Walker-Allgaier, PhD,[a] Oliver Borst, MD,[a] Jörg Kumbrink, PhD,[c,d] Thomas Kirchner, MD,[c,d] Harald Langer, MD,[a] Tobias Geisler, MD,[a] Jürgen Schreieck, MD,[a] Michael Gramlich, MD,[a] Meinrad Gawaz, MD,[a] Peter Seizer, MD[a]

ABSTRACT

BACKGROUND Tachycardiomyopathy or tachycardia-induced cardiomyopathy (TCM) has been known for decades as a reversible form of nonischemic cardiomyopathy. However, its mechanism and properties remain poorly understood.

OBJECTIVES The current study investigated endomyocardial biopsy samples from patients with TCM and compared them with samples from patients with dilated cardiomyopathy (DCM) and inflammatory cardiomyopathy (ICM).

METHODS The study included 189 patients with new-onset heart failure and severely reduced ejection fraction not caused by valvular or ischemic heart disease. Nineteen patients retrospectively fulfilled common criteria of TCM, 79 patients had a diagnosis of DCM, and 91 had a diagnosis of ICM.

RESULTS Patients with TCM, on the basis of clinical criteria, had stronger myocardial expression of major histocompatibility complex class II molecule and enhanced infiltration of $CD68^+$ macrophages compared with patients with DCM. Furthermore, when compared with patients with ICM, the presence of T cells and macrophages was significantly reduced in TCM. Myocardial fibrosis was detected to a significantly lower degree in patients with TCM compared with patients with DCM and ICM. Electron microscopic examination revealed severe structural changes in patients with TCM. A disturbed distribution pattern of mitochondria was predominantly present in TCM. Quantitative assessment of myocyte morphology revealed significantly enhanced myocyte size compared with patients with ICM. Ribonucleic acid expression analysis identified changes in metabolic pathways among the patient groups.

CONCLUSIONS TCM is characterized by changes in cardiomyocyte and mitochondrial morphology accompanied by a macrophage-dominated cardiac inflammation. Thus, further prospective studies are warranted to characterize patients with TCM by endomyocardial biopsy more clearly. (J Am Coll Cardiol 2017;69:2160–72) © 2017 by the American College of Cardiology Foundation.

Histopathologic and immunologic findings

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Histopathological Characteristics of Cardiomyopathy

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Reinhard Kandolf, MD,[b] Antonios Kilias, MD
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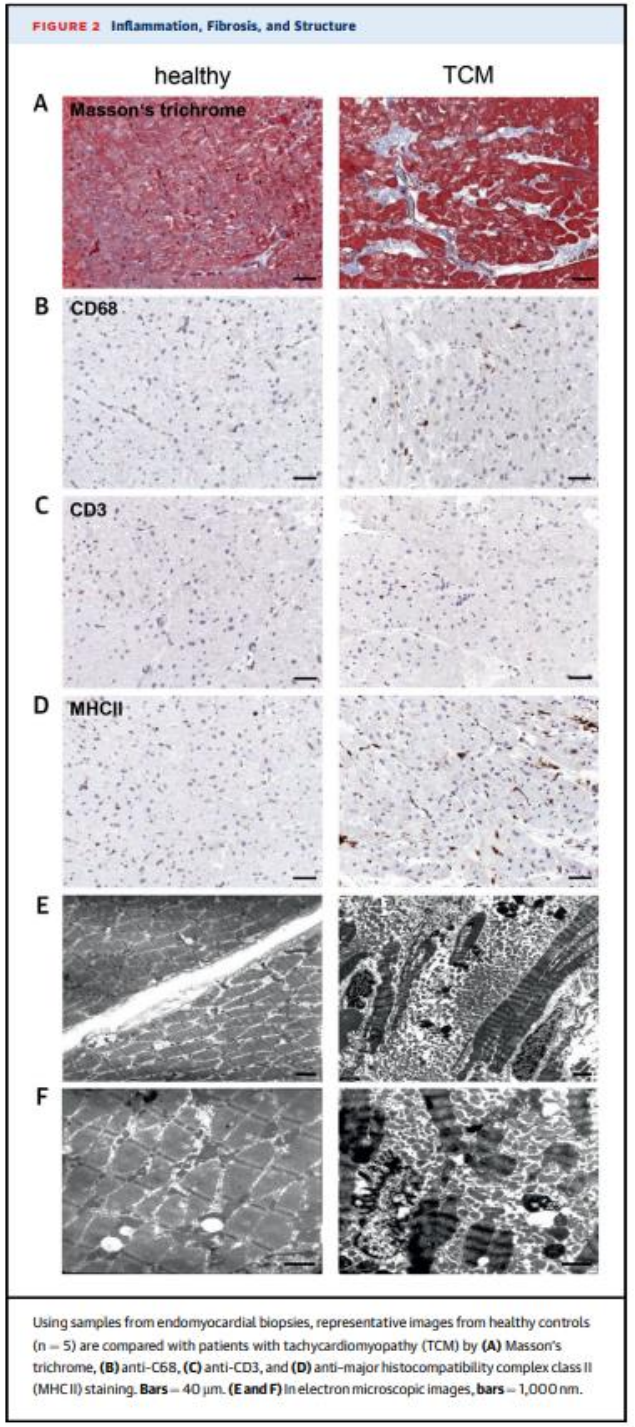

Using samples from endomyocardial biopsies, representative images from healthy controls (n = 5) are compared with patients with tachycardiomyopathy (TCM) by **(A)** Masson's trichrome, **(B)** anti-C68, **(C)** anti-CD3, and **(D)** anti-major histocompatibility complex class II (MHC II) staining. **Bars** = 40 μm. **(E and F)** In electron microscopic images, **bars** = 1,000 nm.

TACHYCARDIA ASSOCIATED WITH TIC

Supraventricular
- Atrial fibrillation (AF)
- Atrial flutter
- Atrial tachycardia
- AV nodal re-entrant tachycardia
- AV re-entrant tachycardia
- Permanent junctional reciprocating tachycardia Junctional ectopic tachycardia

Ventricular
- Idiopathic ventricular tachycardia
- Fascicular tachycardia

Ectopy
- Frequent premature ventricular contractions
- Frequent premature atrial contractions

Pacing Persistent rapid atrial and/or ventricular pacing

Atrial fibrillation

Epidemiologic studies : patients with AF are at increased risk for HF

some pt. : restoration of sinus rhythm
or control of the rapid ventricular rate
-> markedly improves or even normalizes the LVEF
indicating that the LV dysfunction was primarily due to the rapid AF
rather than another etiology.

Am J Med 2002; 113:359.

Atrial flutter

There are less data - frequency and predictors of TIC with atrial flutter
one study : undergoing ablation for atrial flutter

25 % : evidence for cardiomyopathy prior to ablation
Of these, 57 % significant improvement in their LVEF postablation
only predictor of reversibility of cardiomyopathy : average heart rate

Atrial tachycardia

Incessant AT

infrequent cause of symptomatic SVT

can cause myocardial dysfunction in 10 % of pt. J Am Coll Cardiol 2009; 53:1791.

Children are more likely than adults

to present with TIC due to incessant AT

When AT is seen in adults,

m.c. associated with another cardiac problem

Reentrant supraventricular tachycardias

Reentrant SVT,

Am J Cardiol 1986; 57:563.

- atrioventricular nodal reentrant tachycardia (AVNRT) and
- atrioventricular reciprocating tachycardia (AVRT)
- more commonly paroxysmal but can cause a persistent tachycardia

Cases of TIC

- described with persistent junctional reciprocating tachycardia,
- accessory pathway mediated tachycardia (ie, AVRT) and AVNRT

In the absence of other factors

- cardiomyopathy related to an incessant reentrant SVT
- reversible following catheter ablation

Pacing Clin Electrophysiol 1998; 21:2073.

Ventricular arrhythmias

Only rare reports have described reversible cardiomyopathy related to VT,
since this arrhythmia is usually associated with some form of
underlying structural heart disease. Pacing Clin Electrophysiol 1996; 19:42.

However, idiopathic LV tachycardia or right ventricular outflow tract (RVOT)
VT can arise in structurally normal hearts
In rare cases, these are persistent or repetitive
enough to result in a cardiomyopathy

Frequent ventricular ectopy-1

Very frequent ventricular ectopy in the form of PVCs
reversible cardiomyopathy
“frequent" as greater than >15 %
Although some patients with similarly high PVC burdens
can maintain normal cardiac function,
PVC-induced cardiomyopathy has also been reported
in patients with PVC burdens as low as 4 - 5 %

J Cardiovasc Electrophysiol 2011; 22:663.

Frequent ventricular ectopy-2

In a 2014 systematic review and meta-analysis of radiofrequency ablation for the treatment of idiopathic PVCs originating from the RVOT, catheter ablation : associated with a significant improvement in LVEF

Pacing Clin Electrophysiol 2014; 37:73.

Frequent atrial ectopy

Premature atrial complexes (PACs) also referred to as
premature atrial beats,
premature supraventricular complexes, or
premature supraventricular beats
are usually benign,
high burden of PACs
associated with a reversible cardiomyopathy

Pacing Clin Electrophysiol 2012; 35:1232.

Signs and symptoms

The clinical presentation of TIC is variable

Eur Heart J 2021; 42:3599.

but usually involves symptoms of palpitations or HF

present with palpitations or other symptom (dyspnea, chest discomfort)

related to the rapidity or irregularity of their arrhythmia

ECG findings

All patients
    should have an electrocardiogram (ECG)
    to document the cardiac rhythm and ventricular heart rate
Whenever possible, obtaining prior ECGs can be extremely helpful
    to determine whether ambiguous P wave morphologies
    related to the sinus node vs. ectopic atrial focus
No specific ECG findings that distinguish patients with
    TIC and without TIC
ECG findings will vary depending upon the underlying tachyarrhythmia
    TIC heart rate >100 bpm

DIAGNOSTIC TESTING
Cardiac monitoring

Eur Heart J 2020; 41:655.

Heart rate over time
- continuously measured for 24 to 48 hr
- inpatient telemetry or ambulatory (Holter) monitoring
- to document the average heart rate

Sustained HR > 100 bpm, and particularly > 120 bpm
- consistent with TIC

potential reversible nature of TIC
- if uncertainty persists regarding the cardiac rhythm,
- full invasive electrophysiologic studies may be necessary
- to establish the underlying cardiac rhythm and
  - guide the optimal therapy

Assessment of cardiac structure and function

Clin Cardiol 2008; 31:172.

Suspected TIC
- should undergo an assessment of cardiac structure and function
- to document LV size and function, in particular LVEF.

Transthoracic echocardiography
- most common test for documenting cardiac structure and function
- CMR imaging is an alternative approach

No absolute echocardiographic parameters
- that can distinguish TIC from other forms of dilated cardiomyopathy,
- LV end-diastolic dimension tends to be smaller in patients with TIC.

TREATMENT

J Am Coll Cardiol 2015; 66:1714.

Initial treatments for a patient with HF and suspected TIC
same as those used in most other patients with HF with reduced EF
- ACE inhibitors or ARBs,
- Beta blockers
- diuretics and

Tachyarrhythmias
- rate-control medications, consideration of antiarrhythmic drugs and/or cardioversion

However, because of the potentially reversible nature of TIC,
achieve adequate ventricular HR control or to restore sinus rhythm
cardiac resynchronization therapy
or an implantable cardioverter-defibrillator.

Patients with atrial fibrillation or flutter

AF or atrial flutter is the suspected cause of cardiomyopathy
initial approach to management is similar to other patients with HF
includes prompt rate control with AV nodal blockers
& appropriate anticoagulation
Beyond these initial steps, controversy still exists as
to whether rate control or rhythm control

One strategy =

Am J Cardiol 1992; 69:1570.

- minimally symptomatic patients with AF – adequate rate control
  continue medical therapy
  can be effective at improving cardiac function.
- AF who remain significantly symptomatic
  rhythm control strategy.
- atrial flutter, rapid ventricular rates, & newly recognized LV systolic function
  early electrical cardioversion

Patients with another SVT

For supraventricular tachyarrhythmias (SVTs) with TIC
    restoration of sinus rhythm is the usual goal
Options for the restoration of sinus rhythm
    electrical cardioversion,
    antiarrhythmic drugs,
    and catheter ablation.
The initial choice of modality will vary depending upon the underlying SVT
    local expertise and availability of options

If an ablation is performed, close follow-up is required
    because of the tendency for TIC to recur if tachycardia recurs

Patients with frequent ectopy

For patients presenting with a high burden of PVCs
& newly recognized cardiomyopathy,
initial management
look for underlying causes
CAD, valvular heart disease,
arrhythmogenic right ventricular dysplasia (ARVD)
initiation of guideline-based optimal medical therapy for HF.
Correction of electrolytes
initiation of beta blockers

JACC Clin Electrophysiol 2019; 5:537.

TIC in patients with a high PVC burden
(eg, >15 to 20 % on a 24-hr ambulatory monitor)
and associated with LV dysfunction,
-> radiofrequency catheter ablation is attempted.

J Am Coll Cardiol 2018; 72:e91.

Patients with refractory tachyarrhythmias

Supraventricular arrhythmia is likely the cause of cardiomyopathy
and cannot be primarily ablated,
: AV node ablation
+ either biventricular pacing or conduction system pacing

Eur Heart J 2018; 39:3999.

FOLLOW-UP

Initial cardiomyopathy may have taken months to develop,
recurrent tachycardia can lead to an abrupt decline in LVEF.
Diastolic dysfunction can persist even after systolic function has normalized
can lead to decreased coronary flow reserve.
In patients who develop a recurrence of the arrhythmia,
the increased myocardial oxygen demand
in the face of the decreased reserve
can lead to redevelopment of cardiomyopathy
Close ongoing monitoring with clinic visits,
ambulatory (Holter) monitoring, and echocardiography are essential
No guidelines regarding the frequency of monitoring
follow up with patients using a combination of clinic visits,
echocardiography, and
ambulatory monitoring every three to six months for one to two years

Heart Rhythm 2008; 5:1111.

PROGNOSIS

Following the restoration of sinus rhythm or ventricular rate control,
most : significant improvement and/or
normalization of LVEF over a period of months
In some patients whose LVEF has normalized,
the LV chamber may remain somewhat enlarged.
Despite the apparent normalization of cardiac function,
ultrastructural abnormalities of the myocardium may persist.

Circulation 2004; 110:247.

Circ Arrhythm Electrophysiol 2013; 6:697.

Pediatric tachycardia-induced cardiomyopathy

An international multicenter study of pediatric TIC

Children <18 years with incessant tachyarrhythmia,
Cardiac dysfunction(LVEF <50%), and
LV dilation (LVEDD z-score >2)

Heart Rhythm 2014 Jul;11(7):1163-9.

Predictors of myocardial recovery in pediatric tachycardia-induced cardiomyopathy

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BACKGROUND Tachycardia-induced cardiomyopathy (TIC) carries significant risk of morbidity and mortality, although full recovery is possible. Little is known about the myocardial recovery pattern.

OBJECTIVE The purpose of this study was to determine the time course and predictors of myocardial recovery in pediatric TIC.

METHODS An international multicenter study of pediatric TIC was conducted. Children ≤18 years with incessant tachyarrhythmia, cardiac dysfunction (left ventricular ejection fraction [LVEF] <50%), and left ventricular (LV) dilation (left ventricular end-diastolic dimension [LVEDD] z-score ≥2) were included. Children with congenital heart disease or suspected primary cardiomyopathy were excluded. Primary end-points were time to LV systolic functional recovery (LVEF ≥55%) and normal LV size (LVEDD z-score <2).

RESULTS Eighty-one children from 17 centers met inclusion criteria: median age 4.0 years (range 0.0–17.5 years) and baseline LVEF 28% (interquartile range 19–39). The most common arrhythmias were ectopic atrial tachycardia (59%), permanent junctional reciprocating tachycardia (23%), and ventricular tachycardia (7%). Thirteen required extracorporeal membrane oxygenation (n = 11) or ventricular assist device (n = 2) support. Median time to recovery was 51 days for LVEF and 71 days for LVEDD. Two (4%) underwent heart transplantation, and 1 died (1%). Multivariate predictors of LV systolic functional recovery were age (hazard ratio [HR] 0.61, $P = .040$), standardized tachycardia rate (HR 1.16, $P = .015$), mechanical circulatory support (HR 2.61, $P = .044$), and LVEF (HR 1.33 per 10% increase, p=0.005). For normalization of LV size, only baseline LVEDD (HR 0.86, $P = .008$) was predictive.

CONCLUSION Pediatric TIC resolves in a predictable fashion. Factors associated with faster recovery include younger age, higher presenting heart rate, use of mechanical circulatory support, and higher LVEF, whereas only smaller baseline LV size predicts reverse remodeling. This knowledge may be useful for clinical evaluation and follow-up of affected children.

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KEYWORDS Supraventricular tachycardia; Catheter ablation; Antiarrhythmic drugs; Cardiomyopathy; Ventricular remodeling

Pediatric tachycardia-induced cardiomyopathy

Eighty-one children from 17 centers met inclusion criteria

- Median age : 4 years
- baseline LVEF 28%.

most common arrhythmias

- ectopic atrial tachycardia(59%),
- PJRT(23%), and
- ventricular tachycardia(7%)

Thirteen required ECMO(n= 11) or

- ventricular assist device(n=2) support.

Median time to recovery was 51days for LVEF and

- 71days for LVEDD.

Two(4%) underwent heart transplantation, and

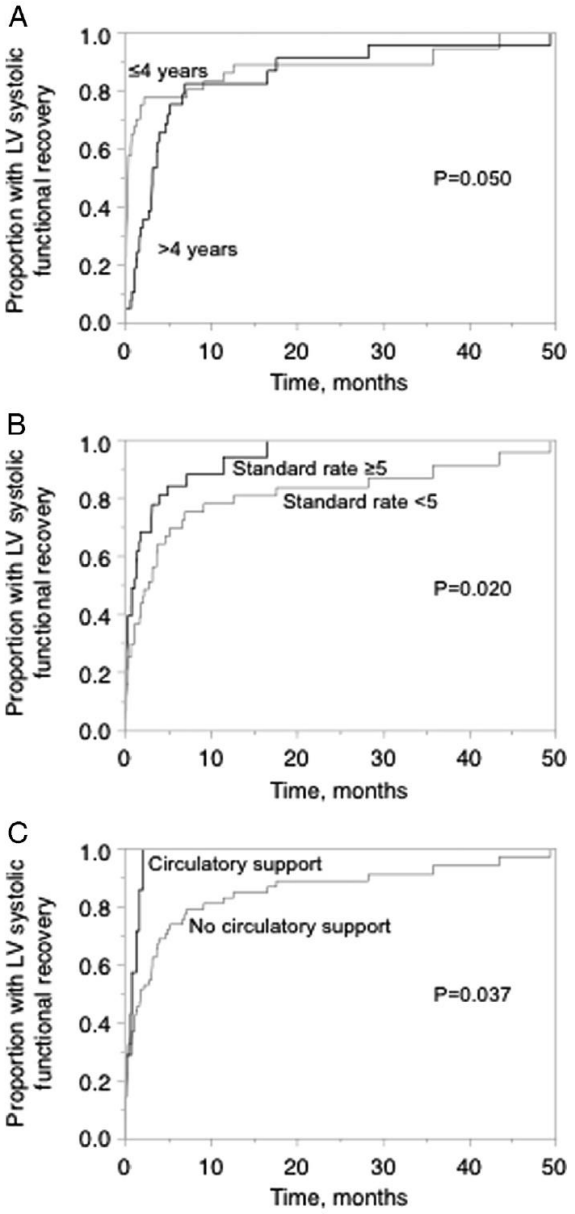
- 1died(1%).

Table 1 TIC population characteristics (N = 81)

Patient data	
Age (years)	4.0 (0.25–11.1)
Male	40 (49%)
Standardized presenting LVEDD	4.3 (3.0–7.2)
Presenting ejection fraction (%)	28 (19–39)
Standardized tachycardia rate	4.8 (3.2–6.2)
Treatment era*	
<2008	37 (46%)
≥2008	44 (54%)
Referred from another institution	41 (51%)
Referring diagnosis	
TIC	26/41 (63%)
Cardiomyopathy	14/41 (34%)
TIC vs cardiomyopathy	1/41 (2%)
Final diagnosis	
EAT	48 (59%)
PJRT	19 (23%)
VT	6 (7%)
AVRT	4 (5%)
Multiple	3 (4%)
CAT	1 (1%)
Referring antiarrhythmic therapy	21 (26%)
Heart failure class	
I	17 (21%)
II	19 (23%)
III	33 (41%)
IV	12 (15%)
Initial management	
Intensive care unit admission	62 (77%)
Inotropic support	39 (48%)
Mechanical circulatory support	13 (16%)
CHF medication	
None	38 (47%)
≥1	43 (53%)

Pediatric tachycardia-induced cardiomyopathy

Factors associated with faster recovery
include younger age,
higher presenting heart rate,
use of mechanical circulatory support, and
higher LVEF,
whereas only smaller baseline LV size
predicts reverse remodeling.



SUMMARY-1

Definition

TIC is a rare cause of a dilated cardiomyopathy
resulting from prolonged periods of rapid ventricular heart rates.
TIC often improves following treatment

Pathophysiology

Chronic tachycardia
produces significant structural changes in the heart,
with LV dilation and cellular morphologic changes

Association with specific arrhythmias

All tachyarrhythmias have been reported to cause TIC, and
frequent ectopic beats have also been associated

SUMMARY-2

Clinical presentation –

TIC is variable but related to

- tachyarrhythmia (palpitations, dyspnea, chest discomfort, ect)
- heart failure (dyspnea, edema, weight gain, orthopnea, etc)

ECG findings –

ECG to document the cardiac rhythm and ventricular heart rate, with comparison to prior ECGs

Treatment –

initial treatments for a patient with HF and suspected TIC

- HF (eg, ACEi or ARBs, BB, diuretics)
- tachyarrhythmias (eg, rate-control medications, antiarrhythmic drugs and/or cardioversion)

Thank you for your attention