

The copyright of this thesis vests in the author. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

Published by the University of Cape Town (UCT) in terms of the non-exclusive license granted to UCT by the author.

**The clinical, electrocardiographic and echocardiographic
features and long-term outcome of patients with
Tachycardia-induced Cardiomyopathy**

by

STUDENT: ASHLEY CHIN

STUDENT NUMBER: CHNASH001

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In fulfilment of the requirements for the degree

Master of Philosophy (MPhil) in Cardiology

Faculty of Health Sciences

UNIVERSITY OF CAPE TOWN

Supervisor: Associate Professor AM Okreglicki

Department of Medicine, University of Cape Town

DECLARATION

I, Dr Ashley Chin, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Dr Ashley Chin

Signed by candidate

Signature Removed

MBChB(UCT), FCP(SA), Cert Cardiology(SA)

Date: 22 October 2010

ABBREVIATIONS

ACE	angiotensin converting enzyme
AF	atrial fibrillation
AFL	atrial flutter
APD	action potential duration
ARVC	arrhythmogenic right ventricular cardiomyopathy
AT	atrial tachycardia
AVNA	atrio-ventricular node ablation
AVNRT	atrio-ventricular nodal re-entry tachycardia
AVRT	atrio-ventricular re-entry tachycardia
bpm	beats per minute
Ca	Calcium
CMO	Cardiomyopathy
DCMO	dilated cardiomyopathy
ECG	electrocardiogram
ERP	effective refractory period
HCM	hypertrophic cardiomyopathy
LA	left atrial
LAH	left atrial hypertrophy
LBBB	left bundle branch block
LV	left ventricular
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
LVIDd	left ventricular internal diameter in diastole
LVIDs	left ventricular internal diameter in systole
MR	mitral regurgitation
MRI	magnetic resonance imaging
NYHA	New York Heart Association
PJRT	permanent junctional reciprocating tachycardia
PPM	permanent pacemaker
PVC	premature ventricular complex
PVI	pulmonary vein isolation
RAAS	renin-angiotensin system
RBBB	right bundle branch block

ROC	receiver operating curve
RVOT	right ventricular outflow tract
RV	right ventricular
Rx	Treatment
TIC	tachycardia-induced cardiomyopathy
VPC	ventricular premature complex
VT	ventricular tachycardia
WPW	Wolff-Parkinson-White

University of Cape Town

ABSTRACT

Introduction

Tachycardia-induced cardiomyopathy (TIC) is a reversible cause of LV systolic dysfunction that can complicate any supraventricular or ventricular tachyarrhythmia. The aim of this study was to characterise the clinical, electrocardiographic and echocardiographic features and long-term outcome of patients with TIC.

Methods

A retrospective study of patients with a diagnosis of TIC at our institution was performed. Pure and impure TIC patients were included in this study if the LVEF at presentation was <50% with an improvement of symptoms and LVEF \geq 5% after control of the causative tachycardia. Clinical, electrocardiographic and echocardiographic data of patients with TIC were obtained from clinic records. Twenty-five pure TIC patients were compared to a control group of 25 DCMO patients matched for age, sex and LVEF. Seventeen pure TIC patients who had recovered LV function after control of the tachycardia were compared to 17 control patients with normal echocardiograms matched for age and LVEF.

Results

Thirty-three patients with pure TIC were identified. There were 25 males and 8 females with a median age of 44 (30-62) years. The causes of pure TIC were AF (n=20), AFL (n=7), AT (n=4), AVNRT (n=1) and fascicular VT (n=1). Twelve patients with impure TIC were identified. There were 9 males and 3 females with a median age of 39 (23-59) years. The nature of the underlying structural heart disease in the impure TIC group was hypertension (n=3), viral myocarditis (n=2), valvular heart disease (n=3), ischaemic heart disease (n=2), patent ductus arteriosus (n=1) and peripartum cardiomyopathy (n=1).

Compared to patients with pure TIC, patients with impure TIC had shorter durations of dyspnoea (p=0.04) and more clinical signs of heart failure at presentation (p=0.003). Patients with impure TIC displayed more electrocardiographic features of underlying structural heart disease [LA hypertrophy (p=0.05), LV hypertrophy (p<0.001) and larger RV₆

voltages ($p=0.04$)]. There were no significant differences in echocardiographic features between the 2 groups.

Compared to patients with DCMO, pure TIC patients were less symptomatic by NYHA class ($p=0.02$), had fewer clinical signs of heart failure ($p=0.007$) and were more likely to report palpitations ($p=0.007$) at presentation. Electrocardiographically, pure TIC patients had less Q waves ($p=0.002$), LV hypertrophy ($p=0.004$), repolarization abnormalities ($p=0.048$) and shorter QRS durations ($p=0.024$). Echocardiographically, pure TIC patients had significantly smaller LVIDd ($p<0.001$), LVIDs ($p=0.001$) and LA dimensions ($p=0.048$) compared to DCMO patients at presentation.

In 6 patients who had a preserved LVEF documented prior to deterioration, LV dysfunction developed over a mean period of 6 (range: 3 to 15) months. The mean LVEF improved significantly from $32.4\pm 9.5\%$ to $53.2\pm 10.5\%$ ($p<0.001$) in the pure TIC group. Both the LVIDd ($p=0.004$) and LVIDs ($p=0.001$) dimensions improved significantly post treatment. The mean LVEF improved significantly from $29.2\pm 10.0\%$ to $55.0\pm 9.9\%$ in the impure TIC group ($p<0.001$). Patients with pure TIC had a trend towards increased residual LVIDd dimensions compared to a control group of normal echocardiograms indicating a persistence of adverse LV remodelling late after control of the causative tachycardia ($p=0.06$). Maximal recovery of LV function was usually noted by 3 to 6 months. In 6 patients, a slower rate of recovery of LV function (over 6 to 12 months) was observed with lenient rate control ($n=4$) and with severe ($LVEF < 20\%$) LV dysfunction ($n=2$). The only predictor of partial recovery of LV function was a longer QRS duration ($p=0.04$). Recurrent tachycardia occurred in 3 patients which resulted in a precipitous decline in LVEF.

Conclusions

This study is the first to compare features of pure and impure TIC. We found that impure TIC may develop more quickly than pure TIC as impure TIC patients have a shorter duration and more severe symptoms at presentation which suggests that underlying structural heart disease is a risk factor in the pathogenesis of TIC. Patients with pure TIC have shorter QRS durations, less LVH, Q waves and repolarization abnormalities at presentation compared to DCMO patients. TIC patients tend to have smaller LVIDd dimensions at presentation and have persistence of adverse LV remodelling as characterised by persistent enlargement of LVIDd dimensions at late follow-up. Patients who have larger LVIDd dimensions at presentation tended to have larger LVIDd dimensions at late follow-up, identifying a subgroup of patients where careful follow-up is required. This study confirms that maximal

improvement of LV function generally occurs by 3 to 6 months. However, we noted slower improvement in LV function over 12 months in patients who had severe LV dysfunction and in patients with AF who had lenient heart rate control. The only predictor of LV improvement was a shorter QRS duration at presentation. We managed to identify 45 patients with this condition over a 15 year period, suggesting that this condition is frequently under-diagnosed and missed.

University of Cape Town

INTRODUCTION

TIC is an important reversible cause of CMO and heart failure. Until recently TIC was considered to be a rare cause of reversible LV dysfunction [1]. However, over the past few years there have been several publications that have established that this disease is much more prevalent than once thought [2, 3].

In the first report of TIC published in 1949, Phillips and Levine concluded that “auricular fibrillation per se may produce cardiac dilatation and progressive congestive heart failure...”[4]. Since that initial description, virtually any supraventricular or ventricular tachycardia including frequent premature ventricular ectopy, have been implicated in the pathogenesis of TIC. However, most reports of TIC have been isolated case reports or small retrospective cohorts comprising less than 20 to 30 patients.

LV dysfunction may either develop in the setting of no underlying structural heart disease, so-called “pure” TIC or in the setting of pre-existing structural heart disease, so called “impure” TIC [5]. TIC studies have mostly enrolled pure TIC patients and have excluded patients with impure TIC. However, impure TIC is probably more common than pure TIC, but less well investigated and reported in the literature.

Interestingly, not all patients exposed to a chronic tachycardia will develop TIC. In the individual patient, the complex interplay of substrate-related factors (genetics and structural heart disease) and tachycardia-related factors (rate, duration and nature of the tachycardia) determine the development of TIC. The presenting clinical, electrocardiographic and echocardiographic features of TIC have not been well described. At presentation, TIC may be indistinguishable from a DCMO with a secondary tachycardia – the so-called “chicken-egg dilemma” [6]. The diagnosis of TIC is usually a retrospective diagnosis made after control of the tachycardia leads to improvement in LV function. Factors influencing the rate and extent of recovery of LV function are poorly understood. Lastly, the long-term outcome and prognosis of patients with TIC have not been well defined.

In order to answer some of these questions, we conducted a retrospective study of TIC at our institution. In this study, we report the clinical, electrocardiographic and echocardiographic features of a relatively large cohort of 45 patients with pure and impure TIC. One of the aims of this study was to identify clinical, electrocardiographic and echocardiographic features that could help the clinician recognise this condition by comparing 25 patients with pure TIC to 25 patients with DCMO. We report on the response

to treatment and compare 17 patients who had normalised LV function after control of the tachycardia with 17 control patients with normal echocardiograms to assess for persistence of adverse LV remodelling. We report on the long-term outcome and prognosis of these patients. Finally, we present a literature review of the topic.

METHODS

Study

We conducted a retrospective study of patients with a diagnosis of TIC who presented to the cardiac clinic at Groote Schuur Hospital, Cape Town, South Africa between 1994 and 2009. The study protocol was approved by the University of Cape Town's Ethics Committee.

Study population

We included patients with a diagnosis of TIC if the presenting LVEF was $<50\%$ and there was an LVEF improvement of $\geq 5\%$ after rate or rhythm control of the tachycardia with medical or ablative therapy. Patients were included in the pure TIC group if no underlying structural heart disease could be identified. Patients with tachycardia-induced LV dysfunction with underlying structural heart disease were included in the impure TIC group and analyzed separately. The cohort of 33 patients with pure TIC was compared to 12 patients with impure TIC. We were able to compare 25 patients with pure TIC with 25 control patients with DCMO (matched for age, sex and presenting LVEF) with regards to clinical, electrocardiographic and echocardiographic parameters. The DCMO patients were obtained from the CMO registry at Groote Schuur Hospital (unpublished data). To assess for persistence of adverse LV remodelling after recovery of LV function, the last available echocardiograms of 17 pure TIC patients who had recovered LV function (post treatment LVEF $\geq 50\%$) were compared to 17 normal echocardiograms matched for age and LVEF. For the purposes of this paper, TIC includes pure and impure TIC unless otherwise specified.

Data collection

Retrospective data collection included clinical, electrocardiographic and echocardiographic characteristics and long-term follow-up of patients diagnosed with pure or impure TIC and matched DCMO controls. Patients diagnosed with TIC during the course of this study were followed prospectively. Patients' clinical records were extensively reviewed. All previous ECGs of patients with TIC were retrieved from an ECG archival system (MUSE CV system) and reviewed to calculate mean heart rate prior to the diagnosis of TIC. All 24-hour Holter monitors performed prior to the diagnosis of TIC were analysed to determine mean and

maximum heart rates during a 24 hour period. Transthoracic echocardiography was performed to measure LVEF, LVIDd, LVIDs, LA size and to quantitate the severity of MR using standard M-mode or modified Simpson's method according to the recommendations of the American Society of Echocardiography. Radionuclide imaging that calculated LVEF was used when available. Serial echocardiograms, if available, were reviewed in patients with TIC to assess the rate and magnitude of LV function improvement. All subsequent visits were reviewed and recurrences of any tachycardias were documented. Patients who had been discharged to follow-up or who were no longer attending the cardiac clinic were telephonically contacted.

Treatment

The choice of treatment of the causative tachycardia was at the discretion of the attending cardiologist. Generally, in patients with AF, rate control using AV nodal blockers (Beta-blockers, Ca-channel blockers), anti-arrhythmic drugs or digoxin was initially preferred. Patients with drug-resistant AF who continued to have poor rate control despite the above treatment, were referred for AVNA and PPM implantation. Catheter ablation was considered first-line therapy for certain arrhythmias (AFL, AT, AVNRT, AVRT and fascicular VT).

Statistical analysis

Results are expressed as mean (standard deviation) or median (interquartile range). Clinical and socio-demographic characteristics of groups studied were compared using the t-test, χ^2 test, Mann-Whitney test or Wilcoxon signed rank test, whichever was appropriate. A p-value of <0.05 was considered significant. Non-parametric tests were used due to the non-normality of some of the variables studied. Receiver operating characteristic (ROC) curves were plotted to examine the diagnostic utility of some variables, which was expressed as an area under the curve and measured using the C-statistic. Data were analysed using SPSS version 17 (Chicago, Illinois; 2009).

RESULTS

Patient demographics, clinical features, investigations, treatment and long-term outcomes of the pure and impure TIC cohort are displayed in Table 1.

Clinical, electrocardiographic and echocardiographic features of pure and impure TIC

The presenting clinical, electrocardiographic and echocardiographic features of the pure and impure TIC cohort are compared in Tables 2A, 2B and 2C respectively. The arrhythmic causes of pure and impure TIC are listed in Table 3.

Pure TIC

The pure TIC cohort consisted of 33 patients (25 males, 8 females). The median age was 44 (30-62) years with marked male predominance (76%). Twenty-one (64%) patients presented with severe effort intolerance (NYHA class III, IV). The median duration of dyspnoea and palpitations prior to presentation was 2 (0.6-7.5) months and 7 (1.3-51.0) months respectively. The arrhythmic causes were AF (n=20), AFL (n=7), AT (n=4), AVNRT (n=1) and fascicular VT (n=1). The most common ECG abnormalities were repolarization abnormalities (55%) followed by LV hypertrophy (12%) and LA hypertrophy (9%). Q waves, LBBB and RBBB were seen in less than 7% of presenting ECGs. The mean LVEF at presentation was 32.4 \pm 9.5%. The mean LVIDd and LVIDs dimensions were 5.7 \pm 0.7cm and 4.8 \pm 0.8cm respectively. The mean LA size was 4.2 \pm 1.0cm.

Impure TIC

The impure TIC cohort consisted of 12 patients (9 males, 3 females). The nature of the underlying structural heart disease was hypertension (n=3), viral myocarditis (n=2), valvular heart disease (n=3), ischaemic heart disease (n=2), patent ductus arteriosus (n=1) and peripartum cardiomyopathy (n=1). The median age was 39 (23-59) years with marked male predominance (75%). Eleven (92%) patients presented with severe effort intolerance (NYHA III, IV). The median duration of dyspnoea and palpitations prior to presentation was 0.5 (0.2-2.0) months and 3 (0.6-4.5) months respectively. The arrhythmic causes were AF (n= 5), AFL (n= 4), AVNRT (n=2) and AVRT (n=1). The most common ECG abnormalities

were repolarization abnormalities (70%) and LV hypertrophy (70%). The mean LVEF at presentation was $29.2 \pm 1.0\%$. The mean LVIDd and LVIDs dimensions were $5.7 \pm 1.0\text{cm}$ and $4.8 \pm 0.8\text{cm}$ respectively. The mean LA size was $4.8 \pm 1.5\text{cm}$.

Comparison between pure and impure TIC

Compared to patients with pure TIC, patients with impure TIC had shorter durations of dyspnoea ($p=0.04$) and more clinical signs of heart failure at presentation ($p=0.003$). Patients with impure TIC displayed more ECG features of underlying structural heart disease [LA hypertrophy ($p=0.05$), LV hypertrophy ($p<0.001$) and larger RV_6 voltages ($p=0.04$)]. There were no significant differences in presenting echocardiographic features between the 2 groups.

Comparison of clinical, electrocardiographic and echocardiographic features of pure TIC and DCMO matched for age, sex and LVEF

In order to identify characteristics that may be useful to differentiate between pure TIC and DCMO at presentation, we compared 25 pure TIC patients with 25 DCMO patients matched for age, sex and LVEF. The clinical, electrocardiographic and echocardiographic features of the 2 groups are displayed in Table 4.

Clinically, pure TIC patients were less symptomatic by NYHA class ($p=0.02$), had fewer clinical signs of heart failure ($p=0.007$) and were more likely to report palpitations ($p=0.007$) at presentation. Electrocardiographically, TIC patients had less Q waves ($p=0.002$), LV hypertrophy ($p=0.004$), repolarization abnormalities ($p=0.048$) and shorter QRS durations ($p=0.024$). Six DCMO patients had underlying paroxysmal or permanent AF. There were no significant differences in the prevalence of LA enlargement, LBBB, RBBB, RV_6 voltage or RV_6/RV_{max} ratio between the 2 groups. Echocardiographically, pure TIC patients had significantly smaller LVIDd ($p<0.001$), LVIDs ($p=0.001$) and LA dimensions ($p=0.048$) compared to DCMO patients at presentation.

Despite significant differences in LVIDd dimensions and QRS duration between the 2 groups, we could not identify any LVIDd dimension or QRS duration that could predict a diagnosis of pure TIC with a high sensitivity and specificity (Graph 1, Graph 2).

Rate of deterioration of left ventricular function

The rate of deterioration of LV function after uncontrolled tachycardia has not been well defined, as most patients will not have had an LVEF documented prior to deterioration. We identified 6 patients who had preserved LV function documented prior to the development of TIC. We noted that LV function in these 6 patients deteriorated over a mean period of 6 months (range: 3 to 15 months). Table 5 displays the causative tachycardia, the average ventricular rate during the tachycardia prior to the diagnosis of TIC, LVEF before TIC, TIC LVEF, medication used and the time period of deterioration.

Pre and post-treatment echocardiographic parameters of pure and impure TIC

The pre and post-treatment echocardiographic parameters of pure and impure TIC are displayed in Table 6. In the pure TIC group, the mean LVEF improved significantly from 32.4 \pm 9.5% to 53.2 \pm 10.5% ($p < 0.001$). Both the LVIDd ($p = 0.004$) and LVIDs ($p = 0.001$) dimensions improved significantly post treatment. There was no significant decrease in LA size pre and post-treatment. In the impure TIC group, the mean LVEF improved significantly from 29.2 \pm 10.0% to 55.0 \pm 9.9% ($p < 0.001$). The LVIDs dimension ($p = 0.04$), but not the LVIDd dimension, improved significantly post treatment. There was no change in LA size pre and post-treatment in the impure TIC group.

Rate of improvement of left ventricular function

We identified variable rates of LV improvement after control of the tachycardia. Thirteen pure TIC patients had at least 3 echocardiograms performed - at initial diagnosis, when improvement of LV function was documented, and at last available follow-up. In 7 (54%) patients, maximal recovery was noted early within the first 3 to 6 months after control of the tachycardia (Graph 3, Group A). However, in 6 (46%) patients, maximal LV improvement occurred late after 6 months with improvement seen even after a year (Graph 4, Group B). Of these 6 patients, 2 patients had LVEF $< 20\%$ and 4 patients had lenient heart rate control as defined by the AFFIRM trial [8] criteria (resting heart rate ≥ 80 bpm) (Table 7).

Comparison of post-treatment echocardiographic parameters of pure TIC with complete LV improvement and normal controls matched for age and LVEF

Seventeen patients with pure TIC who had an improvement of LVEF to >50% after control of the tachycardia were compared to 17 control patients with normal echocardiograms matched for age and LVEF (Table 8). Patients with pure TIC had a trend towards increased residual LVIDd dimensions compared to the control group indicating a persistence of adverse LV remodelling late after control of the causative tachycardia ($p=0.06$). There were no significant differences between the LVIDs and LA dimensions between the 2 groups.

Comparison of pure TIC patients with complete versus partial LV improvement

We compared 22 pure TIC patients who had complete LV improvement (post-treatment LVEF $\geq 50\%$) with 10 pure TIC patients who had partial LV improvement (post-treatment LVEF $< 50\%$) after control of the causative tachycardia to identify predictors of improvement (Table 9). The only predictor of partial improvement was a longer QRS duration at initial presentation which was significantly longer in the group who had partial improvement of LV function ($p=0.04$).

DISCUSSION AND LITERATURE REVIEW

Introduction

The terms tachycardia-induced cardiomyopathy, tachycardia-mediated cardiomyopathy, tachycardia-related cardiomyopathy or tachycardiomyopathy refer to a non-familial cause of DCMO characterised by an impairment of LV systolic dysfunction secondary to a chronic tachycardia or frequent ventricular ectopy which is partially or completely reversible after control of heart rate [7]. Isolated right ventricular dysfunction secondary to ventricular tachycardia has also been reported [8]. According to the number of terms indexed in MEDLINE, the most frequently used term is tachycardia-induced cardiomyopathy.

Subtypes

TIC can be divided into 2 types:

1. "Pure" TIC when a chronic tachycardia results in LV dysfunction in an otherwise normal heart
2. "Impure" TIC when a chronic tachycardia results in LV dysfunction in a patient with underlying structural heart disease

Since this classification was first proposed, it has not been widely adopted [5].

TIC study definitions

No universal definition of TIC exists. Previous studies have used variable TIC definitions. Some studies included patients with a presenting LVEF $\leq 40-45\%$ [9-11]. Other studies have included patients up to LVEF $\leq 50\%$ [12-14]. While most studies have required symptomatic and LV function improvement after control of the tachycardia to make a diagnosis of TIC, the magnitude of improvement of LVEF required to be included in studies has been variable ranging from improvement in LVEF of at least 5% [10] to 15% [9, 11] or an absolute post-treatment LVEF $\geq 50\%$ [13]. Although impure TIC may be more common

than pure TIC, few studies have reported on this entity [15]. In this study, we included all patients with a diagnosis of TIC with a LVEF <50% at presentation with an improvement in symptoms and an LVEF of at least 5% after control of the tachycardia.

Prevalence

The prevalence of TIC is unknown. One study found the entity to be rare cause of DCMO – out of 673 consecutive cases of DCMO, tachycardia was identified as a cause in 1 patient [1]. In a large cohort of unexplained cardiomyopathy and in a prospective registry of cardiovascular disease in Soweto, South Africa, TIC was not reported as a cause of unexplained cardiomyopathy or heart failure in any of the patients [16, 17]. However, studies of drug-refractory AF and LV dysfunction referred for radiofrequency ablation suggest that TIC may have a prevalence rate of 11-30% [3, 18]. The above data suggests that a diagnosis of TIC is frequently under-recognised and missed.

Pathogenesis of TIC

Understanding of the pathogenesis of TIC comes mainly from animal models. Rapid, sustained atrial or ventricular pacing can produce systolic heart failure haemodynamically and neurohumorally similar to heart failure in humans [19]. These animal models of heart failure secondary to rapid pacing were initially developed to produce a reproducible source of animals with CMO [20].

Haemodynamics

In animal models, cardiac output and systemic pressures are reduced after 24 hours of rapid pacing [21]. Elevated filling and pulmonary artery pressures with an increase in systemic vascular resistance are observed after 1 week of rapid pacing. With continued pacing, cardiac output and LVEF worsen over a period of 3 to 5 weeks [16]. Within 48 hours of termination of pacing, cardiac output increases and LV function starts recovering with normalisation after 1 to 2 weeks [22]. Diastolic dysfunction may persist after 4 weeks due to a persistence of structural changes [23]. In swine, rapid LA pacing at 240bpm results in heart failure, 18 to 23 days after pacing [24]. In dogs, rapid RV pacing at 250bpm for 3 to 4 weeks results in heart failure [25].

Structural changes

In animal models, rapid pacing results in dilatation of all 4 cardiac chambers [26]. LV dilatation is more marked for LVIDs than for LVIDd dimensions [27]. Hypertrophy of the walls is not observed with little or no change in myocardial mass [28]. Structural changes may persist at 4 weeks post pacing and end-systolic and end-diastolic volumes may remain elevated at 12 weeks after termination of pacing. Hypertrophy may develop in the 4 weeks after discontinuation of pacing with the accumulation of large collagen fibre bundles [24].

Histological changes

Histological changes occur in the myocyte and in the extracellular matrix. Typically, there is a loss and elongation of myocytes [29, 30]. Disruption of the extracellular matrix results in misalignment of the myofibril and reduction in myocyte attachment to the basement

membrane. There is an increase in B-actin, gamma-actin, alpha-tubulin and matrix metalloproteinases. There is a decreased attachment to laminin, fibronectin, type IV collagen, with disruption of the sarcolemmal interfaces [31]. TGF- β -activin-A SMAD pathway may be involved. In human studies, examination of endomyocardial biopsies with light microscopy displays non-specific findings.

Neurohumoral changes

Neurohumoral activation with increase in ANP, epinephrine, norepinephrine, renin and aldosterone levels is seen [32]. There is a diminished cardiac sympathetic responsiveness to beta-adrenergic stimulation (decrease in B1 receptor density, post-receptor abnormalities of adenylyl cyclase and calcium handling) [33].

Electrical remodelling

Rapid pacing produces alteration in ionic currents – so called electrical remodelling. This is characterised by prolongation of the ventricular action potential duration (APD), effective refractory period (ERP) and QT interval [34]. Mechanisms that result in electrical remodelling are poorly understood. Altered activation sequence even at physiological heart rates can induce electrical remodelling, APD prolongation and ionic current alterations over a short period. There is usually a downregulation of I_{to} , I_{Ks} , I_{K1} currents in ventricular myocytes [35].

Mechanisms

Myocardial energy depletion

Animal studies have shown a depletion in high energy stores (decrease in creatine, phosphocreatine and ATP), diminished activity of the Na/K ATPase pump and mitochondrial injury [36, 37].

Myocardial ischaemia

There is impaired myocardial blood flow and elevated coronary vascular resistance with impaired coronary flow reserve [38]. Ischaemia may be a secondary mechanism in the development of TIC.

Abnormal Calcium cycling

Abnormal cardiac Ca cycling may decrease Ca availability to myocytes with a reduction in cardiac contractility [37, 39].

Oxidative stress

Oxidative stress is increased in experimental tachycardia-induced heart failure models. Probucol, an antioxidant, decreased LV dysfunction and remodelling in a canine model of TIC [40].

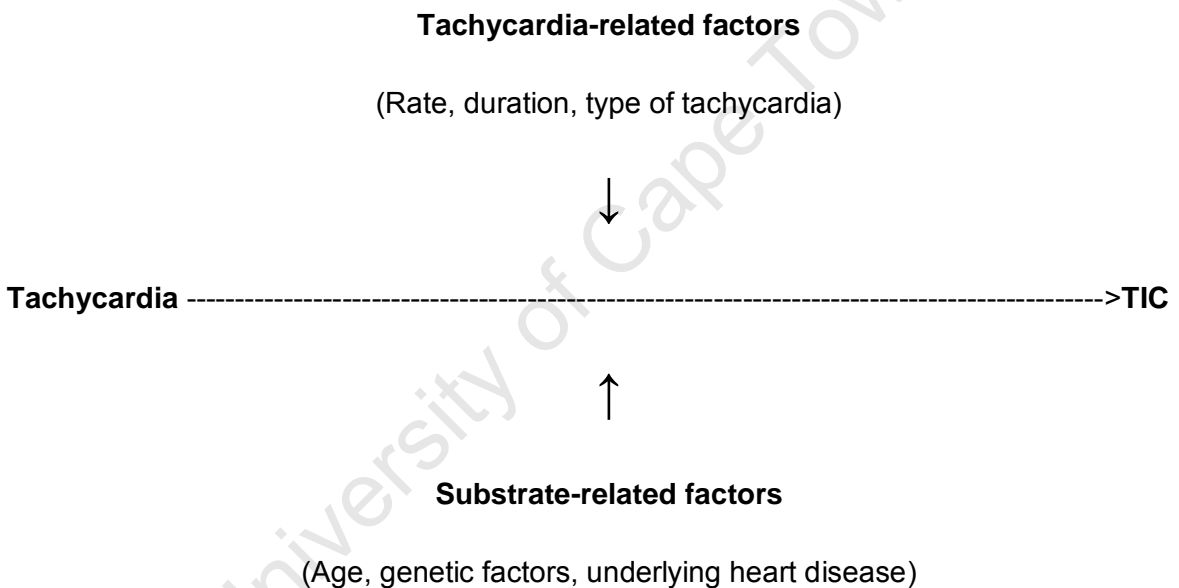
Predictors of development of TIC in animals

In the canine tachycardia experimental model, the response to tachycardia is highly variable. Pacing at a slower rate or for a shorter duration can produce lesser degrees of LV dysfunction [41]. Despite the same pacing rate, some animals developed heart failure symptoms and LV dysfunction after only a short duration of pacing, whereas other animals remain asymptomatic after many weeks of rapid atrial pacing [35]. Ventricular arrhythmias cause a more profound LV dysfunction than supraventricular arrhythmias in dogs [42]. Predictors of TIC in animals remain undefined.

Predictors of development of TIC

Similar to animals, not all patients with a chronic tachycardia will develop TIC. The complex interaction of multiple tachycardia-related factors (including the rate, duration, type of tachycardia) and substrate-related factors (age, genetic factors, underlying structural heart disease) determine the development of TIC (Figure 1).

Figure 1



Tachycardia-related factors

Tachycardia rate

The tachycardia rate needed to cause TIC is unclear. No human studies have prospectively correlated heart rate with the development of TIC. A few studies have determined that any prolonged ventricular rate >100bpm can potentially cause TIC [15, 43, 44]. However, another study of TIC secondary to AF showed that only 50% of patients had a resting ECG with a heart rate >100bpm suggesting that an irregular rhythm without a resting tachycardia

can also potentially cause TIC [3]. Therefore, tachycardia rate is not the only predictor in the pathogenesis of TIC.

In animal studies, ventricular pacing at faster rates leads to quicker deterioration in LV function than ventricular pacing at slower rates. However, in clinical practice, patients with faster ventricular rates usually present earlier with troublesome symptoms and are treated before TIC can develop. This paradox was evident in a recent study of TIC secondary to AT that concluded that slower tachycardia rates are generally better tolerated resulting in patients presenting later, allowing TIC to develop [12].

In our study, 24-hour Holter monitoring was available for analysis in 9 patients (27%) before pure TIC was diagnosed. All 9 patients who developed TIC had an incessant or continuous tachycardia with mean ventricular rates >97 bpm and mean maximum ventricular rates of 174 (range: 145-231) bpm. In patients without Holter monitoring, mean resting ventricular rates in the pure TIC and impure TIC groups were 129 ± 35 (range: 82-240) bpm and 138 ± 33 (range: 95-204) bpm respectively. Our study found, similar to the findings of Packer et al [45], that a faster ventricular rate at presentation did not correlate significantly with a greater severity of LV dysfunction at presentation (Spearman $r = -0.2295$, $P = 0.21$).

There are inherent limitations in measuring mean tachycardia rates that lead to TIC. Firstly, a tachycardia may be paroxysmal and secondly, there may be wide day to day fluctuations in heart rate. A resting pulse rate or a resting ECG is a snapshot in time and is a poor measure of mean heart rate. Patients with apparently well-controlled resting heart rates may have a rapid ventricular response on activity. A 24-hour Holter monitor which records ventricular rates during rest and exercise is a better monitor of mean heart rate but will not account for day-to-day differences in heart rate. Most studies have reported tachycardia rates based on isolated resting ECGs without 24-hour Holter monitoring. In our study, we increased the accuracy of mean heart rate by analysing all ECGs before presentation and all available 24-hour Holter recordings.

Tachycardia duration

The duration of tachycardia needed to cause TIC is unclear. It is difficult to analyse the role of tachycardia duration independent of tachycardia rate and type. In animal studies, rapid atrial or ventricular pacing at very fast rates results in heart failure within 3 to 4 weeks. However, in human studies, it is often the slower tachycardia that can be tolerated for a longer duration allowing TIC to develop insidiously [46]. A few studies have documented

that tachycardias had been present for many years before the index presentation of heart failure [3, 9]. All these studies have highlighted the limitations of determining tachycardia duration based on symptoms alone. It has been stated that chronic or paroxysmal tachycardia occurring more than 10-15% of the day may result in LV dysfunction [5], but little evidence exists to support this statement. Studies have shown that incessant or continuous tachycardias are more likely to cause TIC.

No good measure exists to determine tachycardia duration. In our study, we used duration of palpitations as a marker of tachycardia duration. The median duration of palpitations was 7 (1.3-51.0) and 3 (0.6-4.5) months in the pure and impure TIC groups respectively. In our study, the median duration of tachycardia was shorter than has been published previously [3, 9, 12]. When comparing the pure and impure TIC group, we found no significant difference in the duration of palpitations, but dyspnoea duration was significantly shorter in the impure TIC group, suggesting that progression to heart failure occurs over a few months in patients with underlying structural heart disease with a tachycardia.

Patients may not complain of palpitations in the presence of a tachycardia. Six out of 33 patients (18%) in the pure TIC group did not complain of any palpitations or were unable to define a duration of palpitations. In these patients and in patients with paroxysmal tachycardias, the duration of the tachycardia based on symptoms is difficult to determine. Eleven out of 33 patients (33%) in our study had paroxysmal tachycardias.

In our study, a longer tachycardia duration did not correlate significantly with a greater severity of LV dysfunction at presentation (Spearman $r=0.389384$).

Tachycardia type

Any supraventricular or ventricular tachycardia can potentially cause TIC. The causes of TIC are listed in Table 10. In addition, frequent premature ventricular ectopy and persistent rapid atrial or ventricular pacing have been implicated. In our study we were unable to determine the varying effects of different rhythms on the rate of development of TIC due to the small number of causative tachycardias in some groups.

The type of tachycardia can influence the development of TIC. TIC seems to develop most frequently in patients with AF, PJRT and ventricular ectopy followed by AFL, AT and AVNRT/AVRT.

AF is the most common cause of TIC. In 2 studies, TIC developed in 11/29 (38%) patients with drug-refractory AF with/without heart disease and 9/30 (30%) patients with drug-refractory lone-AF [5, 47]. In a large cohort of 63 patients with LV dysfunction referred for AVNA for drug-refractory AF, TIC developed in 16/63 (25%) patients [18]. In a recent cohort of 366 consecutive patients with AF referred for PVI, 67 (18%) patients had a decreased LVEF <50%. Forty-one (11%) patients developed TIC with an increase in LVEF post ablation >5% [3]. In another study of 19 consecutive patients with drug-refractory AF referred for AV node modification, 12 (63%) had decreased LV function [48]. These studies suggest that TIC is prevalent in a population with drug-refractory AF. The irregular ventricular rhythm of AF may adversely affect LV systolic performance independent of heart rate. Hsu et al demonstrated that even patients with apparent heart rate control during AF on a 48-hour Holter monitor and depressed LV function had improvement in LV function following successful AF ablation [49]. Gentlesk et al further noted that only 50% of TIC patients who showed LV improvement had ECG documentation of heart rates >100bpm [3]. It has been noted that LV function may improve in patients with chronic AF and mean resting heart rates <100bpm and AVNA (Helguera, ACC abstract 1994). Therefore, both rate and regularization of ventricular contraction seem to be important in reversing TIC and AF.

A study of TIC secondary to focal AT showed that TIC developed in 10% of patients with AT [12]. TIC patients who were more likely to be young, male, have incessant tachycardia and longer AT cycle lengths and slower ventricular rates during the tachycardia than those with AT without TIC. In 2 studies of persistent AFL, TIC developed in 11-14% of patients who were referred for an AFL ablation [2, 15]. In another study of 17 patients with incessant AVRT caused by a concealed AP referred for ablation, TIC developed in 7 (41%) patients [50]. These patients were younger and had the tachycardia earlier in life. In a study of 300 patients with AVNRT or AVRT referred for ablation, TIC developed in 14 (<1%) patients [51].

In animal models, ventricular arrhythmias cause more profound depression in LV function than do supraventricular arrhythmias [42, 52]. Frequent premature ventricular ectopy can cause TIC. In a study of 60 consecutive patients with frequent PVC's (>10/hour, 11% of all QRS complexes), LV dysfunction was present in 22 (37%) and in 18 (30%) patients, LV function normalised after successful PVC ablation [53]. Another study by Takemoto et al suggested that RVOT VPC's >20% (20000 VPC's/day) of the day decreased LVEF and increased LV dimensions [54]. In a study by Yarlagadda et al, patients who developed TIC were older than those who did not develop TIC despite having significantly more ventricular ectopy. Patients who developed TIC occurred even in patients with 5500 VPC's/day [55].

In a study of 174 consecutive patients referred for ablation of frequent idiopathic PVC's, a PVC burden (percentage of total beats that were PVC's) of >24% was strongly associated with a PVC-induced cardiomyopathy with a sensitivity and specificity of 80%. No patients developed a cardiomyopathy in this study with a PVC burden < 10%. The PVC burden (and not site of origin of ectopy) was the only independent predictor of development of a cardiomyopathy [56].

University of Cape Town

Substrate factors

Genetic factors

An intriguing aspect of the development of TIC is the role of underlying genetic susceptibility. In alcoholic CMO, there seems to be an underlying genetic basis for the observation that only some patients will develop an alcoholic CMO if exposed to chronic alcohol use. A DD ACE genotype increased the risk of developing an alcoholic CMO by a factor of 14 [57]. This observation has led some to postulate that ACE gene I/D polymorphisms may account for the CMO secondary to a tachycardia [58]. The DD ACE genotype was significantly more common in patients with TIC than controls and the ID ACE genotype.

Underlying structural heart disease

It is unknown whether patients who have underlying structural heart disease are at more or less risk of developing TIC. It has been observed that patients with underlying structural heart disease may develop TIC more quickly [5]. Our study supports this observation. We noted that patients with impure TIC reported a shorter duration of dyspnoea and were more symptomatic compared to patients with pure TIC. This observation suggests that patients with underlying structural heart disease may develop LV dysfunction more quickly and present earlier with symptoms and signs of heart failure. The observation that a recurrence of a tachycardia in a TIC patient who has recovered LV function leads to a precipitous decline in LV function supports the above observation [9].

Gender

Many, but not all, studies have shown a strikingly male predominance in the development of TIC [2, 3, 9, 11, 14, 15, 44, 53]. Whether this association is causative or simply reflects referral bias is unclear.

Rate of deterioration of left ventricular function

The complex interplay of all the above variables results in marked variability in the rate of development of TIC and the rate deterioration of LV function.

For example, a patient with no pre-existing heart disease may tolerate a slow supraventricular tachycardia for years and may present years after the onset of the tachycardia as compared to a patient with underlying structural heart disease who may deteriorate more quickly and present within months with symptoms.

Many studies have reported a slow insidious rate of development of TIC, typically over months to years from the onset of tachycardia or symptoms of palpitations. However, the same studies highlight the limitations of determining the duration of the tachycardia based on symptoms alone. Moreover, baseline echocardiograms confirming preserved LV function predating the tachycardia are often unavailable in individual patients making the precise rate of deterioration of LV function difficult to determine.

In our study, we observed that although a tachycardia had been documented for many months or years, when LV dysfunction ensues, rapid deterioration in LV function can occur over a period of a few months. We noted in 5 patients with pure TIC, who had preserved LV function documented prior to the development of TIC that, although the palpitations had been present for a mean of 50 months, LV function deteriorated rapidly over a mean period of 6 months when the tachycardia was poorly controlled. In 1 patient with impure TIC who had a recurrence of the tachycardia, the LV function deteriorated over a period of 1 month. This highlights the importance of prompt effective rate or rhythm control of a tachycardia before LV dysfunction ensues.

Diagnosis

TIC is a diagnosis of exclusion. A definite diagnosis of TIC requires measurement of LV function prior to the onset of uncontrolled tachycardia and documentation of worsening LV function in the setting of the tachycardia with improvement in LV function after control of the ventricular rate. However, most patients will not have had LV function measured prior to the start of the tachycardia and therefore the diagnosis can only be made retrospectively after LV function improves with control of the tachycardia. It is important to remember that frequent ventricular ectopy has also been implicated. Therefore, TIC should be suspected in any patient with clinical or investigational evidence of impaired LV function, with or without underlying pre-existing structural heart disease, in the setting of any supraventricular or ventricular tachycardia and/or frequent ventricular ectopy.

Clinical features

The clinical presentation of TIC is highly variable. Presentations range from asymptomatic LV dysfunction to severe advanced heart failure with a wide spectrum of presentations in-between. Many patients will not complain of palpitations and most will present with heart failure symptoms. Recognising a tachycardia or ventricular ectopy in the setting of LV dysfunction is the clue to diagnosis. It is important to remember that TIC can develop in patients with or without pre-existing structural heart disease, congenital or acquired. TIC can present at any age, including the foetus to the elderly.

The most common foetal tachyarrhythmias are atrioventricular re-entry tachycardia caused by an accessory pathway (90% of foetal supraventricular tachycardia) and atrial flutter. Ventricular tachycardia and atrial fibrillation are rarely detected in utero. Persistent foetal tachycardias should be promptly treated with anti-arrhythmic drugs given transplacentally or via direct foetal transfer to treat hydrops foetalis. In one study of foetal tachycardias, non-hydrops foetuses had a very good prognosis (mortality rate 4%) with transplacental treatment with anti-arrhythmic drugs. Although most arrhythmias associated with hydrops foetalis could be controlled by transplacental treatment, the mortality rate was much higher at 27% [59].

In our study, patients with pure TIC generally had a better effort tolerance (NYHA class), complained of more palpitations and had fewer clinical signs of heart failure at presentation

compared to patients with DCMO. However, a wide range of clinical presentations were seen. The range included patients who had a normal effort tolerance and no signs of heart failure to patients with severe advanced heart failure who were considered for cardiac transplantation. In these cases, it was difficult to determine whether the tachycardia was causal or secondary to the CMO on clinical grounds. Documentation of AF that predates LV dysfunction by months/years may be a useful pointer to a diagnosis of TIC as AF tends to develop late in the course of DCMO [60]. In our control group, only 6 out of the 25 (25%) patients with DCMO were in AF. Patients with impure TIC had generally a shorter duration and more severe symptoms at presentation.

Electrocardiographic features

To our knowledge, the electrocardiographic characteristics of TIC have not been previously reported. In our study, we found that TIC patients had shorter QRS durations and were less likely to have Q-waves, LVH and repolarization abnormalities compared to patients with DCMO.

A previous study showed that certain electrocardiographic features may be useful for differentiating between DCMO and ischaemic CMO [61]. DCMO was characterised by higher RV_6 voltages and higher RV_6/R_{max} (leads I, II or III) ratios. The authors stated that RV_6 voltage is determined by the distance from the LV to the RV_6 chest lead and is a marker of LV dilatation. Limb voltages in leads I, II, III are not affected by the distance of the LV to the chest wall and are markers of voltage producing cardiac mass. In patients with DCMO, replacement fibrosis or infiltrates reduce R wave voltages in these limb leads. When we compared TIC patients with DCMO patients, there were no significant differences in RV_6 voltages and RV_6/R_{max} ratios between the 2 groups. By inference RV_6 voltages and RV_6/R_{max} ratios may be useful parameters to distinguish between DCMO or TIC from ischaemic CMO but not useful to distinguish between DCMO and TIC.

Echocardiographic features

A previous study by Jeong et al showed that TIC patients tended to have smaller LV mass indices, volume dimensions and LV dimensions compared to patients with DCMO [11]. They suggested that a $LVIDd \leq 6.1$ cm at presentation predicted TIC with a sensitivity of 100% and a specificity of 71%. Our study confirmed that pure TIC patients had significantly smaller $LVIDd$, $LVIDs$ and LA dimensions when compared to DCMO patients at

presentation. However, in contrast to their study, we could not confirm a LVIDd dimension that predicted TIC with a high degree of sensitivity and specificity. In our study, secondary MR was common. MR was often mild to moderate in severity and tended to improve after control of the tachycardia. An animal sheep study of TIC showed that MR resulted from decreased leaflet coaptation secondary to annular dilatation in the septal-lateral direction [62]. Subvalvular leaflet tethering does not seem to play a major role in the pathogenesis of MR presumably because TIC patients may have preserved LV size and volumes.

MRI features

There are few published reports of TIC who have undergone MRI. MRI is known to be a useful tool to differentiate between DCMO, HCM, ARVC and non-compaction CMO. The MRI characteristics of TIC needs further study. We report the MRI findings of 1 patient with TIC secondary to AFL who underwent MRI at presentation. She had LV chamber enlargement with elevated end-systolic and diastolic volumes, LVEF 39%, and 3 dyskinetic segments. She had no features of fibrosis on delayed contrast enhancement. After AFL ablation, her LV function improved over 6 months. An interesting aspect for further research would be to investigate the prognostic value of MRI in predicting LV function improvement. Hypothetically, longstanding TIC may have higher degrees of delayed contrast enhancement reflecting extensive fibrosis of the ventricles on MRI which may predict lesser degrees of LV improvement after control of the tachycardia.

Dobutamine stress echocardiography

A study by Paelinck et al suggested that low-dose dobutamine stress echocardiography (DSE) can be used to predict improvement in LVEF in patients with CMO and AF after conversion to sinus rhythm [63]. Patients who showed an increase in LVEF with DSE were more likely to improve LVEF after correction to sinus rhythm and be diagnosed with TIC.

Management

Management of TIC is essentially twofold. Firstly, aggressive control or stopping of the tachycardia is essential. Secondly, standard heart failure drugs including Beta-Blockers (if tolerated), ACE-inhibitors or angiotensin-receptor blockers should be prescribed. The best means to achieve heart rate control vary depending on the type of arrhythmia. A recent guideline on the management of TIC has been published [64]. All the recommendations are based on expert opinion or small case studies.

Radiofrequency ablation is considered first-line therapy in most arrhythmias resulting in TIC. In patients with AF, either a rate or rhythm control strategy can be applied. Medical therapy to slow ventricular rate or prevent recurrences, prior to radiofrequency ablation, or if radiofrequency is unavailable, should be tried but may not be effective.

Rate or rhythm control for AF?

What remains unclear is whether a rate or rhythm control strategy is better in AF-induced TIC. The results of the AF-CHF trial conducted in patients with AF and LV dysfunction showed that there was essentially no difference between a rate and rhythm control strategy [65]. However, these results may not be directly applicable to TIC. Another study by Hsu et al favoured a rhythm control strategy showing that LV function improved even in patients with apparent well-controlled heart rates [49]. Recently, pulmonary vein isolation was shown to be effective in patients with AF and depressed LVEF in reversal of TIC [3].

Rate control

Rate control of AF can be achieved by AV nodal blockers (Beta-Blockers, Calcium-channel blockers, digoxin), anti-arrhythmic therapy (amiodarone, sotalol) or if medication is ineffective, AVNA and PPM implantation. However, what constitutes “successful” rate control is unclear and is not evidence-based. In the AFFIRM trial, rate control was defined as a resting heart rate ≤ 80 bpm and either a maximum of ≤ 110 bpm during a 6 minute walk test or a mean < 100 bpm on 24-hour Holter monitoring, with the rate not exceeding 110% of maximum predicted age-adjusted exercise rate [66]. The RACE trial used a simpler definition of ≤ 100 bpm [67], while HOTCAFE required a resting heart rate 70 to 90 bpm and ≤ 140 bpm during moderate exercise [68].

In our study, we noted in 4 patients with AF that although pharmacological rate control was suboptimal (according to the AFFIRM trial criteria), LV function improved in all patients at a slower rate over a year (Graph 2, Group B and Table 7). In contrast, we noticed that in patients who had AVNA/PPM implanted for failed pharmacological rate control, the LV function generally had maximal improvement by 3 to 6 months. These findings suggest that although strict rate control is required for optimal LV recovery, lenient rate control may still result in improvement. In the RACE II trial, a randomized trial of optimal heart rate control versus lenient heart rate control in patients with permanent AF found no difference between the 2 strategies [69]. However, TIC patients were underrepresented in this trial. It remains unclear whether TIC patients may benefit from stricter heart rate control and, therefore, clinicians should still aim for rate control according to the above AFFIRM criteria.

Rhythm control

Rhythm control can be achieved by pharmacological or electrical cardioversion, antiarrhythmic drugs or catheter ablation of AF. AF burden is defined as the total percent of time a patient is in AF which is determined by the number and duration of AF episodes. A major reduction in the frequency and duration of symptomatic AF episodes is an acceptable endpoint [70].

Anti-failure treatment

There is currently no recommendation as to how long to continue with anti-failure treatment. Studies have shown that although the LVEF may normalise post treatment, adverse LV remodelling persists as suggested by elevated LVIDd dimensions compared to controls [10]. This observation suggests without firm evidence that RAAS-inhibitors and Beta-Blockers should probably be continued in TIC patients with persistent LV dysfunction and/or LV dilatation.

Follow-up

Patients with TIC require careful follow-up. Recovery may be unpredictable and close observation is required in these patients. Recurrence of the tachycardia can result in a precipitous decline in LV function and one report has suggested that the risks of sudden cardiac death is increased [9].

Recovery of left ventricular function

In animal studies, impaired LV function improves within 48 hours of cessation of pacing and returns to normal by 1 to 2 weeks. In human studies, however, LV recovery takes months to years and is usually unpredictable. Factors such as the severity and duration of LV dysfunction, presence of pre-existing structural heart disease and extent of control of the tachycardia determine the degree and rate of LV recovery.

Degree of recovery

The degree of recovery of LV function after control of the causative tachycardia can range from complete, partial to totally absent. It is likely that TIC involves a spectrum extending from a “stunned” myocardium with complete reversibility to a “burnt-out” phase which is irreversible.

A study by Luchsinger et al showed that patients with AFL with LV dysfunction who did not improve post ablation had a worse LVEF and NYHA functional class before ablation compared to patients who had improvement of LV function [15]. This study reported that severe LV dysfunction secondary to AFL was a predictor of partial or no improvement presumably because severe LV dysfunction may be secondary to irreversible myocardial damage. There was no difference in age or AFL duration between those who improved and those who did not. In contrast, another study of patients with AFL found that a rapid ventricular rate during AFL was the only independent predictor of reversibility of the CMO [2]. In this study, 75% of patients with a heart rate >100bpm improved compared to only 25% of patients with a ventricular response less than 100bpm. The observation that a higher percentage of non-responders occurred in studies that included patients with underlying structural heart disease [2, 3, 15] compared to studies that have excluded underlying heart disease [12, 51] suggests that pre-existing structural heart disease may be a predictor of a poor response.

In our study, severe LV dysfunction at presentation was not a predictor of partial improvement of LV function after control of the tachycardia. In 8 out of 12 (75%) patients with severe LV dysfunction (LVEF <30%), LVEF improved to $\geq 50\%$. However, we found that patients who had severe symptomatic (NYHA III, IV) heart failure at presentation tended to have lesser degrees of LV improvement ($p=0.041$). There was no correlation between the LVIDd at presentation and the degree of recovery of LV function ($r=-0.1408$, $p=0.554$).

Theoretically, patients with a longer duration of LV dysfunction and/or duration of the tachycardia may have partial improvement because of long-standing irreversible damage. We were unable to investigate whether long-standing LV dysfunction predicted poorer recovery as it was difficult to determine how long patients had tachycardia-induced LV dysfunction. We did note, however, in 3 patients (patient 8, patient 29, patient 32) who had a history of 10 to 20 years of AF, despite initial pharmacological rate control and later AVNA/PPM implantations, that recovery of LV function was incomplete at late follow-up.

In order to identify predictors of LV improvement, we compared patients who had partial LV improvement (LVEF <50%) with patients who had recovered LV function (LVEF ≥50%) at last follow-up. Patients who had partial improvement had significantly wider QRS durations at presentation which presumably reflects widespread permanent underlying structural damage.

Rate of recovery

Some studies have indicated that LV function improvement is expected within a few days to weeks after rate or rhythm control of the underlying tachycardia, followed by a slower rate of improvement that reaches its maximum after 3 to 6 months [5, 9, 71]. Some studies have also noted that patients with severe tachycardia-mediated injury may have greater improvement at late follow-up compared to early follow-up [45, 51].

In our study, we observed that maximal recovery of LV function was usually achieved by 3 to 6 months, with little improvement noted after 6 months. In patients who had severe LV dysfunction or who had lenient rate control, improvement occurred over a 6 to 12 months period. These findings suggest that prompt rate or rhythm control of the tachycardia is necessary for optimal LV extent and rate of recovery. However, lenient rate control may lead to improvement but at a slower rate.

Left ventricular remodelling

In animal studies, although LV systolic function recovers rapidly after cessation of pacing, diastolic dysfunction, fibrosis and cellular Ca alterations persist and LV hypertrophy develops during the recovery phase. Persistent structural abnormalities may persist in patients who have severe chamber dilatation or have a prolonged duration of the tachycardia [72]. This is supported by histological studies that have documented myocardial fibrosis even in patients who have recovered LV function [73]. LV hypertrophy after recovery is not recognised in human studies. Echocardiographic evaluation of diastolic function after normalisation of LV function has not been reported.

One study showed that although the LVEF improved significantly with control of the tachycardia, LV dimensions and volumes remain significantly elevated when compared to control patients late after control of the tachycardia [10]. In our study, when we compared TIC patients who had complete improvement, with age and LVEF matched control subjects with normal echocardiograms, TIC patients had a trend towards greater LVIDd dimensions, indicating persistence of adverse LV remodelling at follow-up. Similar to previous studies, we noted a significant decrease in the LVIDd and LVIDs dimensions post treatment [3, 51]. In other studies, the increase in LVEF was mainly due to a decline in end-systolic dimension, whereas the end-diastolic diameter was not significantly changed [44, 50]. In our study, LA dimensions remain significantly elevated at follow-up, suggesting persistence of adverse atrial remodelling and providing a potential substrate for atrial arrhythmias.

In our study, TIC patients with dilated ventricles at presentation were more likely to have residual LV dilatation at follow-up ($r=0.68$, $p=0.002$, Graph 5). This observation stresses the importance of repeated echocardiographic measurements at follow-up and the prescription of Beta-blockers and RAAS inhibitors to prevent adverse ventricular remodelling in all TIC patients if tolerated. In particular, patients with dilated ventricles at presentation should be followed up carefully as they are more likely to have dilated ventricles at late follow-up. There have been no studies investigating the long-term role of Beta-blockade and RAAS-inhibitors in patients with TIC and after control of the tachycardia. Until further data becomes available, it would be reasonable to continue Beta-blockade and RAAS-inhibitors indefinitely in all patients who have LV dysfunction and/or LV dilatation at follow-up.

Recurrence of tachycardia

Nerheim et al reported 5 patients with recurrent tachycardia which caused a rapid decline in LV function and development of heart failure in all patients [9]. These patients had an abrupt fall in LVEF within 6 months and reversed again within a similar period. Since that initial observation, another study reported 2 patients with recurrence of the tachycardia and TIC [14]. Notably, these 2 patients had a very short period of symptoms from the tachyarrhythmia (12 days, 1 day) to presentation. Our study is the third report with recurrent tachycardias occurring in 3 patients.

Patient 1 developed an impure TIC secondary to an orthodromic AVRT with a previous inferior myocardial infarction. The presenting LVEF was 21%. He was started on metoprolol, enalapril and diuretics. At a 3 week follow-up visit, his symptoms had markedly improved with a repeat echocardiogram showing a LVEF of 51%, confirming a diagnosis of TIC. Unfortunately, he defaulted medical therapy and presented with recurrence of the AVRT 4 months later. An echocardiogram confirmed that his LV function had deteriorated to a LVEF of 35%. His accessory pathway was successfully ablated. At 2 year follow-up, he reported no recurrences of palpitations or AVRT. His last follow-up echocardiogram showed a LVEF of 47%. This case highlights the observation that recurrence of tachycardia may lead to a rapid decline in LV function.

Patient 4 developed a pure TIC secondary to 2 different ATs with a presenting LVEF of 16%. Only one of the ATs could be ablated. Nevertheless, the LVEF improved to 61% 1 year after ablation. The patient was continued on antiarrhythmic therapy. Eighteen months later, the first AT recurred with a deterioration in LVEF to 50% with mean heart rates on Holter of 119bpm. Pharmacological rhythm control was preferred. At last follow-up the LVEF had improved to 53%.

Patient 23 developed a pure TIC secondary to rapid AFL with a presenting LVEF of 40%. While awaiting ablation of the AFL, the LVEF improved to 50% with pharmacological rate control. AFL ablation was unsuccessful. His AFL persisted and pharmacological AFL rate control (mean heart rates 97bpm) was noted to be suboptimal. This led to a slow progressive decline in LV function over 3 years (LVEF 32%). Successful AFL ablation led to improvement in LV function to LVEF of 53% 5 months after ablation. This last case demonstrates that LV function may gradually deteriorate over time, if rate control is suboptimal.

Prognosis and long-term follow-up

The long-term prognosis of TIC has not been established. Nerheim et al documented 3 TIC patients who had recovered LV function and had sudden cardiac death [9]. A study by Fujino [13], showed that cardiac death and recurrent hospitalisations were significantly less in the TIC group than a DCMO group.

In our study, 33 pure TIC patients were followed up for a mean period of 6.8 (range: 1 to 19) years. Twenty patients were confirmed alive at the time of writing this paper. There were 3 confirmed deaths. The nature of the 1 death was due to a cholangiocarcinoma. The causes of death in the other 2 patients could not be determined from clinical records. Ten out of 33 patients could not be contacted. Of the 10 patients, 4 were discharged in a stable condition from the cardiac clinic. Three patients were discharged in a stable condition to other hospitals around South Africa. Three patients did not return for routine follow-up visits. We cannot exclude sudden cardiac deaths in patients who were not confirmed to be alive. In contrast, 14 out of 25 patients were alive in the DCMO control group. As a large number of TIC patients were lost to follow-up, we could not make a meaningful comparison with DCMO patients regarding long-term prognosis and outcome. To our knowledge, there have been no reports of secondary ventricular arrhythmias in patients with resolved TIC.

LIMITATIONS

This is a retrospective study with a small number of TIC patients. The patients represent a select group of non-consecutive patients referred to a regional referral hospital. It is likely that a sizeable number of patients with TIC were not included in this study. The true prevalence of TIC in patients with tachycardia can only be answered by a prospective study or CMO registry.

Although care was taken to examine all ECGs prior to presentation to calculate average heart rate, this may not be a true reflection of average heart rate during a 24 hour period. An accurate duration of the tachycardia before presentation was difficult to determine. Patients cannot always recall the exact duration of palpitations and patients could have a tachycardia for a variable length of time before an ECG is performed.

Not all patients with pure TIC had coronary angiography to exclude coronary artery disease, although no coronary intervention was performed between presentation and when LV function had recovered to account for improvement in LV function.

Not all patients at presentation had echocardiography performed in sinus rhythm. The calculation of LV systolic function in the presence of a shortened diastolic filling time may result in an underestimate of LVEF. In this study we were unable to control for the effects of differences in heart rate or rhythm in the assessment of LV function at initial presentation and after control of the tachycardia. Unfortunately, heart rate and rhythm at the time of initial LV assessment at echocardiography were not routinely recorded on echocardiography or radionuclide imaging reports at our institution. However, echocardiographic reports at slower heart rates were preferentially recorded for LV function assessment for better accuracy of LV function. When more than one echocardiogram was performed in short succession, an average of the LVEF and LV dimensions were calculated from serial echocardiograms to improve accuracy. In some cases, echocardiography was not performed at our institution. Echocardiography and interpretation of ECGs were often the interpretation of one cardiologist.

The small control group of 25 DCMO patients was limited by the number of DCMO patients available in the CMO registry. Treatment of tachycardia varied between cardiologists and was not administered uniformly. The long-term prognosis of TIC could not be accurately determined because a large number of patients were lost to follow-up

who were not contactable. There was no standard follow-up time. Not all patients had repeat echocardiograms and echocardiograms were performed at variable time periods.

CONCLUSIONS

This is one of the largest retrospective studies of TIC and the first large series from Africa. This study is the first to compare features of pure and impure TIC. We found that impure TIC may develop more quickly than pure TIC as impure TIC patients have a shorter duration and more severe symptoms at presentation. This observation suggests that underlying structural heart disease is a risk factor in the development of TIC. This study reports the first description of ECG findings of TIC. Patients with pure TIC have shorter QRS durations, less LVH, Q waves and repolarization abnormalities at presentation compared to DCMO patients. This is the second study to report that TIC patients have smaller LVIDd dimensions at presentation and have persistence of adverse LV remodelling as characterised by persistent enlargement of LVIDd dimensions at late follow-up. Patients who have larger LVIDd dimensions at presentation tended to have larger LVIDd dimensions at late follow-up, identifying a subgroup of patients where careful follow-up is required. This study confirms that maximal improvement of LV function generally occurs by 3 to 6 months. However, we noted slower improvement in LV function over 12 months in patients who had severe LV dysfunction and in patients with AF who had lenient heart rate control. The only predictor of LV improvement was a shorter QRS duration at presentation. We managed to identify 45 patients with this condition at a large regional referral centre in Cape Town over a 15 year period, suggesting that this condition is frequently under-diagnosed and missed.

ADDENDUM

TABLES 1-10

GRAPHS 1-5

University of Cape Town

TABLE 1:

Cohort of pure and impure TIC patients

Patient	Age (years)	Sex (M/F)	NYHA (Class)	Dyspnoea duration (months)	Palpitations (Yes/No)	Palpitations duration (months)	Rhythm	Heart rate (bpm)	Initial LVEF	Last LVEF	Treatment	Recurrent TIC	Alive
Pure TIC													
Patient 1	30	F	3	1	Yes	1	AT	197	14%	53%	Medical Rx	No	
Patient 2	20	M	2	2	Yes	2	AT	136	42%	47%	AT ablation	No	
Patient 3	62	M	3	1	Yes	1	AF	89	30%	50%	AVNA/PPM	No	No
Patient 4	30	F	3	2	Yes	8	AT	128	16%	53%	Medical Rx	Yes	Yes
Patient 5	68	M	3		Yes	6	AFL	148	35%	85%	AFL ablation	No	Yes
Patient 6	42	M	3	2	Yes	60	AFL	102	38%	60%	AFL ablation	No	Yes
Patient 7	52	F	2	3	Yes	3	AF	156	45%	54%	Medical Rx	No	Yes
Patient 8	46	M	3	96	No		AF	100	21%	36%	AVNA/PPM	No	Yes
Patient 9	45	M	1	0	Yes	240	AFL/AF	102	49%	67%	AVNA/PPM	No	Yes
Patient 10	40	M	2	3	Yes	3	AFL	165	13%	63%	AVNA/PPM/AFL ablation	No	Yes
Patient 11	54	M	3	12	Yes		AF, previous AFL	84	22%	+	Medical Rx, AFL ablation	No	Yes
Patient 12	28	M	2	1	Yes	1	AF	123	27%	35%	AVNA/PPM	No	
Patient 13	38	M	4		Yes		AF		30%	63%	Medical Rx	No	
Patient 14	68	F	3	1	Yes	1	AVNRT	132	30%	40%	AVNRT ablation	No	Yes
Patient 15	17	F	3	2	Yes	2	AT	131	23%	40%	Medical Rx	No	Yes
Patient 16	47	F	3	12	Yes	24	AF	126	48%	59%	AVNA/PPM	No	Yes
Patient 17	56	M	2	9	Yes	3	AFL	123	33%	64%	AFL ablation	No	Yes
Patient 18	33	F	1	0	No		AF/WPW	240	33%	41%	WPW ablation	No	
Patient 19	41	M	3	1	No		AF	133	22%	49%	AVNA/PPM	No	Yes
Patient 20	65	M	4	8	No	0	AF	136	23%	60%	AVNA/PPM	No	No
Patient 21	46	M	3	1	Yes	11	AFL	144	31%	51%	AFL ablation	No	Yes
Patient 22	79	F	3	1	No	0	AF	167	30%	50%	Medical Rx/AVNA/PPM	No	
Patient 23	38	M	1	0	Yes	6	AF/AFL	82	40%	53%	Medical Rx/AFL ablation	Yes	
Patient 24	16	M	4	0	Yes	0	Fascicular VT	178	29%	56%	VT ablation	No	Yes
Patient 25	47	M	3	12	Yes	108	AFL	95	37%	58%	AFL ablation/medical Rx	No	Yes
Patient 26	64	M	3	6	Yes	72	AFL/AF	105	37%	50%	AFL ablation/medical Rx	No	Yes
Patient 27	50	M	2		Yes	60	AF	100	41%	50%	AVNA/PPM	No	
Patient 28	71	M	3	24	No	0	AF/AFL	130	35%	41%	AFL ablation	No	
Patient 29	62	M	4	3	Yes	120	AF	133	39%	45%	AVNA/PPM	No	Yes
Patient 30	57	M	3	36	Yes	144	AF/AFL	102	40%	50%	AVNA/PPM	No	
Patient 31	48	M	1	0	Yes		AFL	150	42%	65%	AFL ablation	No	Yes
Patient 32	55	M	2		Yes	6	AF	86	35%	49%	Medical Rx	No	Yes
Patient 33	66	M	3	12	Yes	12	AF	93	38%	64%	AVNA/PPM	No	No
Impure TIC													
Patient 34	37	F	2		Yes	0	AFL	66	38%	43%	AVNA/PPM	No	Yes
Patient 35	53	M	3				AFL	96	35%	48%	Medical Rx	No	
Patient 36	62	M	3	1	No	6	AF/AFL	102	31%	47%	Medical Rx	No	
Patient 37	40	F	4	0	No		Atypical AVNRT	72	27%	64%	AVNRT ablation	No	Yes
Patient 38	52	M	4	0			AF		48%	67%	AVNA/PPM	No	Yes
Patient 39	63	M	3		Yes	144	AF	114	42%	54%	AVNA/PPM	No	Yes
Patient 40	35	M	3		Yes	12	AF	126	30%	47%	AVNA/PPM	No	Yes
Patient 41	56	M	3	0	Yes	3	AVRT	94	21%	48%	AVRT ablation	Yes	Yes
Patient 42	20	M	3	1	Yes	1	Atypical AFL	72	20%	51%	Medical Rx	No	Yes
Patient 43	39	M	4	3	Yes	3	AF/AFL	136	19%	64%	AFL ablation	No	
Patient 44	25	F	4	0	Yes	0	AFL	78	17%	72%	AVNA/PPM	No	Yes
Patient 45	28	M	4	1	Yes	1	AVNRT	84	22%	*	AVNRT ablation	No	

See abbreviation table
 * LVEF not documented, but improvement noted
 <blank> unknown

TABLE 2A:**Patient demographics and clinical features of pure and impure TIC**

Patient demographics and clinical features	Pure TIC group (n=33)	Impure TIC group (n=12)	P value
Age (years)	44 (30-62)	39 (23-59)	0.26 ¶
Sex (no. (%))			0.96 *
Male	25 (75.8%)	9 (75.0%)	
Female	8 (24.2%)	3 (25.0%)	
NYHA (no. (%))			0.11 *
NYHA I,II	10 (30.3%)	1 (8.3%)	
NYHA III, IV	21 (63.6%)	11 (91.7%)	
Unknown	2 (6.1%)	0 (0.0%)	
Dyspnoea duration (months)	2 (0.6-7.5)	0.50 (0.2-2.0)	0.04 ¶
Palpitations duration (months)	7 (1.3-51.0)	3 (0.6-4.5)	0.45 ¶
Signs of heart failure (no. (%))			0.003 *
Yes	15 (45.5%)	9 (75.0%)	
No	18 (54.5%)	1 (8.3%)	
Unknown	0	2 (16.7%)	

¶ Mann-Whitney Test

* Chi-Square Test

TABLE 2B:**Electrocardiographic features of pure and impure TIC**

ECG features	Pure TIC group (n=33)	Impure TIC group † (n=10)	P value *
Sinus Rhythm			0.21
Yes	6 (18.2%)	3 (30.0%)	
No	27 (81.8%)	7 (70.0%)	
LA hypertrophy			0.05
Yes	3 (9.1%)	3 (30.0%)	
No	6 (18.2%)	0 (0.0%)	
Unable to assess	24 (72.7%)	7 (70.0%)	
Q waves			0.67
Yes	2 (6.1%)	1 (10.0%)	
No	31 (93.9%)	9 (90.0%)	
LBBB			0.43
Yes	2 (6.1%)	0 (0.0%)	
No	31 (93.9%)	10 (100.0%)	
RBBB			0.58
Yes	1 (3.0%)	0 (0.0%)	
No	32 (97.0%)	10 (100.0%)	
LV hypertrophy			<0.001
Yes	4 (12.1%)	7 (70.0%)	
No	29 (87.9%)	3 (30.0%)	
Repolarization abnormalities			0.39
Yes	18 (54.5%)	7 (70.0%)	

No	15 (45.5%)	3 (30.0%)	
QRS width (ms)	92 (71-152)	102 (72-117)	0.20 ¶
RV ₆ (mV)	1.5+/-0.7	1.6+/-0.3	0.04]
RV ₆ /Rmax	1.8+/-0.7	2.1+/-0.8	0.78]

† The ECGs of 2 patients with impure TIC were unavailable for analysis

¶ Mann-Whitney Test

* Chi-Square Test

] T-test

University of Cape Town

TABLE 2C:

Echocardiographic features of pure and impure TIC

Echocardiographic features	Pure TIC group (n=33)	Impure TIC group (n=12)	P value]
LVEF (%)	32.4+/-9.5	29.2+/-1.0	0.80
LVIDd (cm)	5.7+/-0.7	5.7+/-1.0	0.06
LVIDs (cm)	4.8+/-0.8	4.8+/-0.8	0.76
LA size (cm)	4.2+/-1.0	4.8+/-1.5	0.30

] T-test

TABLE 3:**Arrhythmic causes of pure and impure TIC**

Causative tachycardia	Pure TIC group (n=33) n (%)	Impure TIC group (n=12) n (%)
Atrial fibrillation	20 (60.6%)	5 (41.7%)
Typical atrial flutter	6 (18.2%)	3 (25.0%)
Atrial tachycardia	4 (12.1%)	0 (0.0%)
Atypical atrial flutter	1 (3.0%)	1 (8.3%)
AVNRT	1 (3.0%)	2 (16.7%)
AVRT	0 (0.0%)	1 (8.3%)
Fascicular VT	1 (3.0%)	0 (0.0%)

TABLE 4:**Comparison of clinical, electrocardiographic and echocardiographic features of pure TIC and DCMO matched for age, sex and LVEF**

Patient demographics and clinical features	Pure TIC group (n=25) n (%)	DCMO group (n=25) n (%)	P value *
Age	46 (16-67)	46 (21-65)	0.846 ¶
Sex			1.00
Male	19 (76%)	19 (76%)	
Female	6 (24%)	6 (24%)	
NYHA			0.02
NYHA I, II	9 (36%)	4 (16%)	
NYHA III, IV	16 (64%)	21 (84%)	
Palpitations			0.007
Yes	21 (84%)	12 (48%)	
No	4 (16%)	13 (52%)	
Signs of heart failure			0.007
Yes	12 (48%)	21 (84%)	
No	13 (52%)	4 (16%)	
ECG features			
Sinus Rhythm			<0.001
Yes	5 (20%)	19 (76%)	
No	20 (80%)	6 (24%)	
LA enlargement			0.546
Yes	3 (12%)	8 (32%)	
No	5 (20%)	11 (44%)	
Unable to assess	17 (68%)	6 (24%)	
Q waves			0.002
Yes	1 (4%)	10 (40%)	
No	24 (96%)	15 (60%)	

LBBB			0.123
Yes	2 (8%)	6 (24%)	
No	23 (92%)	19 (76%)	
RBBB			0.5
Yes	1 (4%)	0 (0%)	
No	24 (96%)	25 (100%)	
LVH			0.004
Yes	4 (16%)	14 (56%)	
No	21 (84%)	11 (44%)	
Repolarization abnormalities			0.048
Yes	16 (64%)	22 (88%)	
No	9 (36%)	3 (12%)	
QRS width (ms)	88 (82-102)	100 (92-110)	0.024 ¶
RV ₆ (mm)	15.8+/-7.5	15.0+/-11.2	0.79]
RV ₆ /Rmax	1.84+/-0.8	1.69+/-1.2	0.63]
Echocardiographic features			
LVEF (%)	30.8+/-9.5	27.8+/-10.2	0.29]
LVIDd (cm)	5.7+/-0.7	6.6+/-0.6	<0.001]
LVIDs (cm)	4.9+/-0.8	5.7+/-0.6	0.001]
LA size (cm)	4.1+/-1.0	4.6+/-0.5	0.048]

¶ Mann-Whitney Test

* Chi-Square Test

] T-test

TABLE 5:**Patients showing rate of deterioration of left ventricular function**

Patient (no.)	Causative tachycardia	Average ventricular rate during tachycardia (bpm)	LVEF before TIC (%)	TIC LVEF (%)	Medication	Time period of deterioration (months)
Patient 3	AF	89	"Normal"	30	Digoxin	3-8
Patient 6	AFL	102	76	38	Beta-Blocker, digoxin	4
Patient 7	AF	156	"Slightly depressed"	27	Digoxin, verapamil	15
Patient 21	AFL	144	71	31	Beta-Blocker	7
Patient 27	AF	100	55	41	Digoxin, verapamil	3
Patient 29	AF	133	71	47	Beta-Blocker, amiodarone	11

TABLE 6:

Pre and post-treatment echocardiographic parameters of pure and impure TIC

	Pure TIC At presentation (n=33)	Pure TIC Post- treatment (n=33)	P value]		Impure TIC At presentation (n=12)	Impure TIC Post- treatment (n=12)	P value]
LVEF (%)	32.4+/-9.5	53.2+/-10.5	<0.001		29.2+/-10.0	55.0+/-9.9	<0.001
LVIDd (cm)	5.7+/-0.7	5.3+/-0.8	0.004		5.7+/-1.0	5.5+/-0.8	0.86
LVIDs (cm)	4.8+/-0.8	3.6(2.2-4.6)	0.001 ¶		4.8+/-0.8	3.8(2.7-4.4)	0.04 ¶
LA size (cm)	4.2+/-1.0	4.1+/-0.8	0.19		4.81+/-1.5	4.7+/-1.3	0.92

] T-test

¶ Mann-Whitney Test

University of Cape Town

TABLE 7:

Pure TIC patients with lenient heart rate control and late improvement of left ventricular function

Patient (no.)	Average resting heart rate on treatment (bpm)
Patient 33	111
Patient 1	92
Patient 15	100
Patient 4	96

University of Cape Town

TABLE 8:

Post-treatment echocardiographic parameters of pure TIC patients with complete LV improvement and normal controls matched for age and LVEF

	Pure TIC group (n=17)	Normal Controls (n=17)	P value [†]
LVEF (%)	58.9+/-8.9	60.4+/-9.2	0.5
LVIDd (cm)	5.2+/-0.6	4.8+/-0.5	0.06
LVIDs (cm)	3.5+/-0.5	3.2+/-0.6	0.18
LA size (cm)	4.2 +/- 0.7	3.9 +/-0.5	0.19

[†] T-test

University of Cape Town

TABLE 9:**Comparison of pure TIC patients with complete versus partial LV improvement**

	Pure TIC group with complete LV improvement (LVEF \geq 50%) (n=22)	Pure TIC group with partial LV improvement (LVEF <50%) (n=10)	P value *
Age	49.4+/-14.7	44.1+/-19.6	0.40 ¶
Sex			0.66
Male	17 (77.3%)	7 (70.0%)	
Female	5 (22.7%)	3 (30.0%)	
NYHA			0.77
NYHA I, II	7 (31.8%)	3 (30.0%)	
NYHA III, IV	15 (68.2)	5 (50.0%)	
Unknown	0 (0.0%)	2 (20.0%)	
Palpitations			0.085
Yes	20 (90.9%)	6 (60.0%)	
No	2 (9.1%)	3 (30.0%)	
Unknown	0 (0.0%)	1 (10.0%)	
Signs of heart failure			0.631
Yes	9 (40.9%)	5 (50.0%)	
No	13 (59.1%)	5 (50.0%)	
Sinus Rhythm			0.80
Yes	4 (18.2%)	2 (20.0%)	
No	18 (81.8%)	7 (70.0%)	
Unknown	0 (0.0%)	1 (10.0%)	
LA enlargement			0.62
Yes	6 (27.3%)	3 (30.0%)	
No	6 (27.3%)	3 (30.0%)	
Unable to assess	10 (45.6%)	4 (40.0%)	
Q waves			0.112
Yes	0 (0.0%)	1 (10.0%)	

No	22 (100.0%)	8 (80.0%)	
Unknown	0 (0.0%)	1 (10.0%)	
LBBB			0.88
Yes	2 (9.1%)	1 (10.0%)	
No	20 (91.9%)	8 (80.0%)	
Unknown	0 (0.0%)	1 (10.0%)	
RBBB			0.52
Yes	1 (4.5%)	0 (0.0%)	
No	21 (95.5%)	9 (90.0%)	
Unknown	0 (0.0%)	1 (10.0%)	
LVH			0.13
Yes	4 (18.2%)	4 (40.0%)	
No	18 (81.8%)	5 (50.0%)	
Unknown	0 (0.0%)	1 (10.0%)	
Repolarization abnormalities			0.40
Yes	11 (50.0%)	6 (60.0%)	
No	11 (50.0%)	3 (30.0%)	
Unknown	0 (0.0%)	1 (10.0%)	
QRS width (ms)	90.2+/-12.9	106+/-28.5	0.04]
LVEF (%)	33.8+/-10.3	30.7+/-7.3	0.41]
LVIDd (cm)	5.7+/-0.7	5.7+/-0.8	0.97]
LVIDs (cm)	4.8+/-0.9	4.9+/-0.7	0.83]
LA size (cm)	4.1+/-1.4	4.3+/-0.6	0.71]

¶ Mann-Whitney Test

* Chi-Square Test

] T-test

TABLE 10:

Causes of TIC

Supraventricular

Atrial fibrillation

Atrial flutter

Atrial tachycardia

Atrio-ventricular nodal re-entry tachycardia

Atrio-ventricular re-entry tachycardia

Inappropriate sinus tachycardia

Permanent junctional reciprocating tachycardia

Ventricular

Right ventricular outflow tract tachycardia

Fascicular tachycardia

Bundle branch re-entry tachycardia

Ectopy

Premature ventricular ectopics

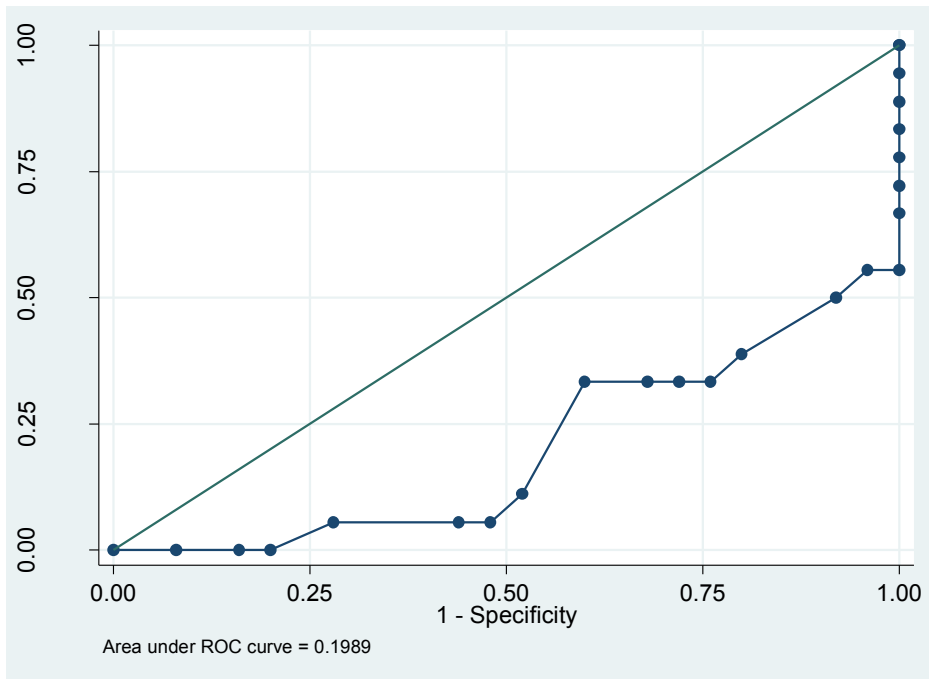
Pacing

Rapid atrial or ventricular pacing

GRAPHS

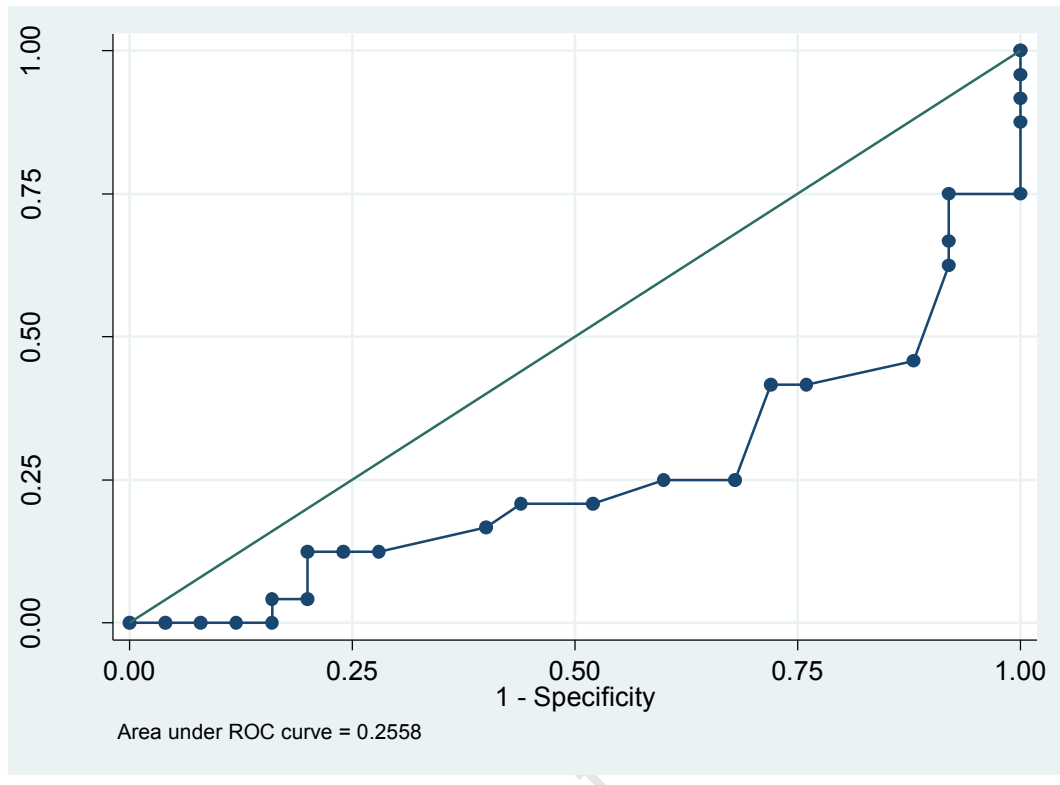
GRAPH 1

The ROC curve analysis of LVIDd dimensions according to LVEF in the TIC and DCMO groups



GRAPH 2

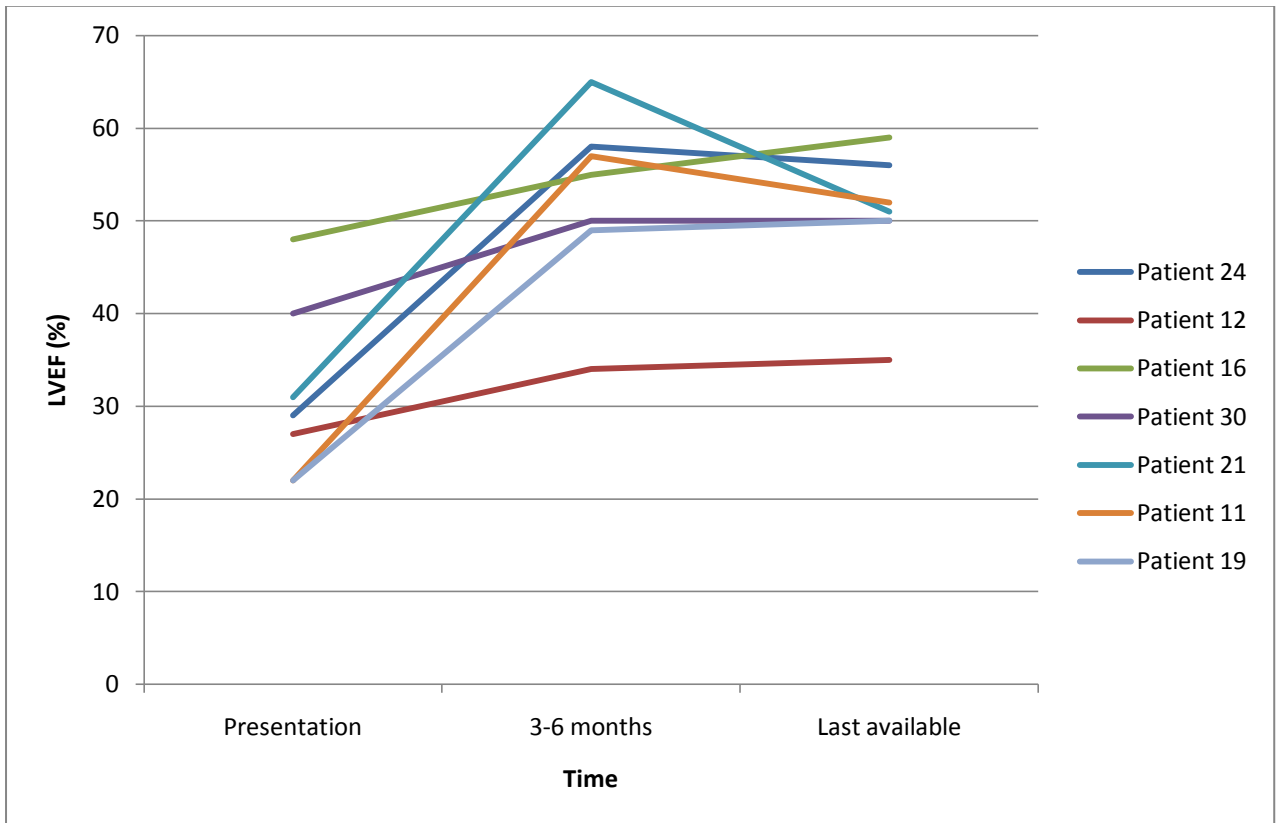
The ROC curve analysis of QRS duration according to LVEF in the TIC and DCMO groups



University of

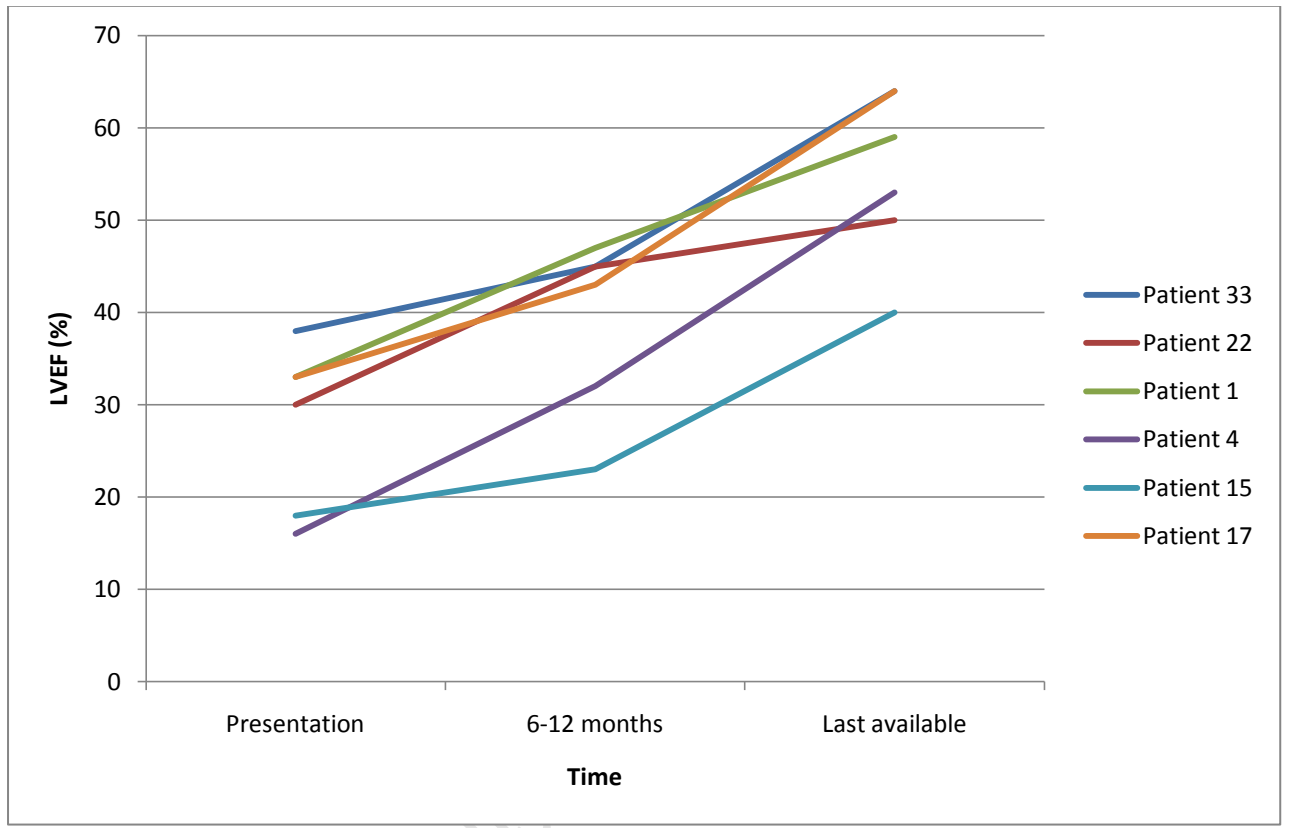
GRAPH 3:

Group A (Early recovery)



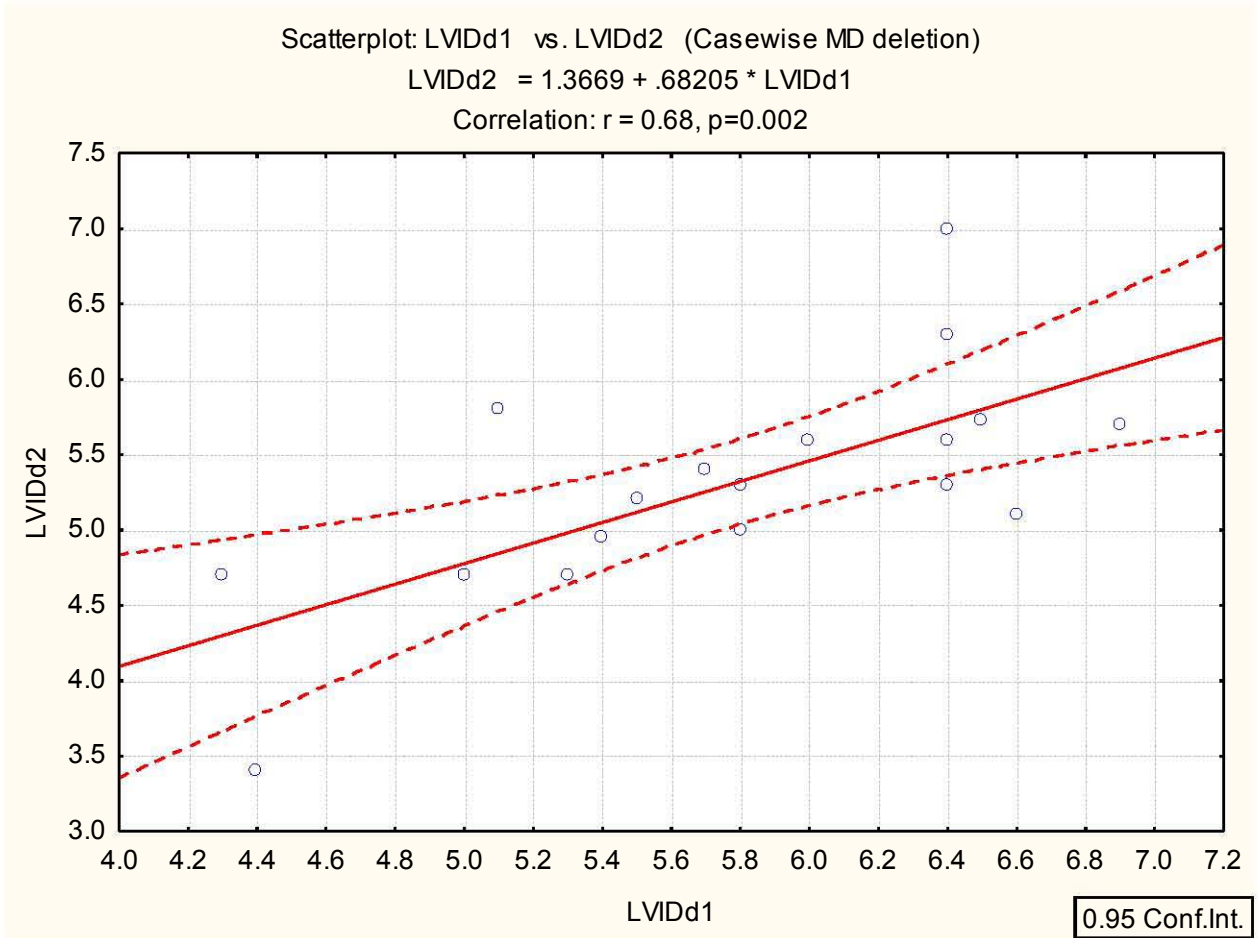
GRAPH 4:

Group B (Late recovery)



GRAPH 5:

Scatterplot of LV dimensions at presentation and last available follow-up



ACKNOWLEDGEMENTS

I would like to thank Professor AM Okreglicki, Professor R Scott Millar, Dr NB Ntusi, Dr V Thomas and Dr M Badri for their individual contributions to this study and to Professor PJ Commerford and Professor BM Mayosi for their support and motivation.

I dedicate this thesis to my wife, Cindy and to my 2 daughters, Kathryn and Emily.

University of Cape Town

REFERENCES

1. Kasper, E.K., et al., *The causes of dilated cardiomyopathy: a clinicopathologic review of 673 consecutive patients*. J Am Coll Cardiol, 1994. **23**(3): p. 586-90.
2. Pizzale, S., et al., *Frequency and predictors of tachycardia-induced cardiomyopathy in patients with persistent atrial flutter*. Can J Cardiol, 2009. **25**(8): p. 469-72.
3. Gentlesk, P.J., et al., *Reversal of left ventricular dysfunction following ablation of atrial fibrillation*. J Cardiovasc Electrophysiol, 2007. **18**(1): p. 9-14.
4. Phillips, E. and S.A. Levine, *Auricular fibrillation without other evidence of heart disease; a cause of reversible heart failure*. Am J Med, 1949. **7**(4): p. 478-89.
5. Fenelon, G., et al., *Tachycardiomyopathy: mechanisms and clinical implications*. Pacing Clin Electrophysiol, 1996. **19**(1): p. 95-106.
6. Gallagher, J.J., *Tachycardia and cardiomyopathy: the chicken-egg dilemma revisited*. J Am Coll Cardiol, 1985. **6**(5): p. 1172-3.
7. Elliott, P., et al., *What do tachycardiomyopathy belong to? Reply*. Eur Heart J, 2008.
8. Massoure, P.L., et al., *Tachycardia-induced right ventricular cardiomyopathy: epicardial radiofrequency ablation of an unusual and unexpected ventricular tachycardia*. J Cardiovasc Electrophysiol, 2009. **20**(7): p. 813-7.
9. Nerheim, P., et al., *Heart failure and sudden death in patients with tachycardia-induced cardiomyopathy and recurrent tachycardia*. Circulation, 2004. **110**(3): p. 247-52.
10. Dandamudi, G., et al., *Persistent left ventricular dilatation in tachycardia-induced cardiomyopathy patients after appropriate treatment and normalization of ejection fraction*. Heart Rhythm, 2008. **5**(8): p. 1111-4.
11. Jeong, Y.H., et al., *Diagnostic approach and treatment strategy in tachycardia-induced cardiomyopathy*. Clin Cardiol, 2008. **31**(4): p. 172-8.

12. Medi, C., et al., *Tachycardia-mediated cardiomyopathy secondary to focal atrial tachycardia: long-term outcome after catheter ablation*. J Am Coll Cardiol, 2009. **53**(19): p. 1791-7.
13. Fujino, T., et al., *Characteristics of congestive heart failure accompanied by atrial fibrillation with special reference to tachycardia-induced cardiomyopathy*. Circ J, 2007. **71**(6): p. 936-40.
14. Watanabe, H., et al., *Clinical characteristics, treatment, and outcome of tachycardia induced cardiomyopathy*. Int Heart J, 2008. **49**(1): p. 39-47.
15. Luchsinger, J.A. and J.S. Steinberg, *Resolution of cardiomyopathy after ablation of atrial flutter*. J Am Coll Cardiol, 1998. **32**(1): p. 205-10.
16. Felker, G.M., et al., *Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy*. N Engl J Med, 2000. **342**(15): p. 1077-84.
17. Sliwa, K., et al., *Spectrum of heart disease and risk factors in a black urban population in South Africa (the Heart of Soweto Study): a cohort study*. Lancet, 2008. **371**(9616): p. 915-22.
18. Redfield, M.M., et al., *Tachycardia-related cardiomyopathy: a common cause of ventricular dysfunction in patients with atrial fibrillation referred for atrioventricular ablation*. Mayo Clin Proc, 2000. **75**(8): p. 790-5.
19. Shinbane, J.S., et al., *Tachycardia-induced cardiomyopathy: a review of animal models and clinical studies*. J Am Coll Cardiol, 1997. **29**(4): p. 709-15.
20. Moe, G.W. and P. Armstrong, *Pacing-induced heart failure: a model to study the mechanism of disease progression and novel therapy in heart failure*. Cardiovasc Res, 1999. **42**(3): p. 591-9.
21. Wilson, J.R., et al., *Experimental congestive heart failure produced by rapid ventricular pacing in the dog: cardiac effects*. Circulation, 1987. **75**(4): p. 857-67.
22. Moe, G.W., et al., *Early recovery from heart failure: insights into the pathogenesis of experimental chronic pacing-induced heart failure*. J Lab Clin Med, 1988. **112**(4): p. 426-32.

23. Moe, G.W., et al., *Left ventricular remodelling and disparate changes in contractility and relaxation during the development of and recovery from experimental heart failure*. Cardiovasc Res, 1994. **28**(1): p. 66-71.
24. Tomita, M., et al., *Changes in left ventricular volume, mass, and function during the development and regression of supraventricular tachycardia-induced cardiomyopathy. Disparity between recovery of systolic versus diastolic function*. Circulation, 1991. **83**(2): p. 635-44.
25. Armstrong, P.W., et al., *Rapid ventricular pacing in the dog: pathophysiologic studies of heart failure*. Circulation, 1986. **74**(5): p. 1075-84.
26. Scott, B.D., et al., *Cardiac geometry and mass changes associated with pacing-induced cardiomyopathy in the dog*. Am Heart J, 1993. **125**(4): p. 1047-53.
27. Howard, R.J., et al., *Recovery from heart failure: structural and functional analysis in a canine model*. Can J Physiol Pharmacol, 1988. **66**(12): p. 1505-12.
28. Howard, R.J., G.W. Moe, and P.W. Armstrong, *Sequential echocardiographic-Doppler assessment of left ventricular remodelling and mitral regurgitation during evolving experimental heart failure*. Cardiovasc Res, 1991. **25**(6): p. 468-74.
29. Kajstura, J., et al., *The cellular basis of pacing-induced dilated cardiomyopathy. Myocyte cell loss and myocyte cellular reactive hypertrophy*. Circulation, 1995. **92**(8): p. 2306-17.
30. Spinale, F.G., et al., *Relation between ventricular and myocyte remodeling with the development and regression of supraventricular tachycardia-induced cardiomyopathy*. Circ Res, 1991. **69**(4): p. 1058-67.
31. Zellner, J.L., et al., *Alterations in myocyte shape and basement membrane attachment with tachycardia-induced heart failure*. Circ Res, 1991. **69**(3): p. 590-600.
32. Moe, G.W., et al., *Alterations in serum sodium in relation to atrial natriuretic factor and other neuroendocrine variables in experimental pacing-induced heart failure*. J Am Coll Cardiol, 1989. **13**(1): p. 173-9.

33. Calderone, A., et al., *Dysfunction of the beta- and alpha-adrenergic systems in a model of congestive heart failure. The pacing-overdrive dog.* *Circ Res*, 1991. **69**(2): p. 332-43.
34. Libbus, I. and D.S. Rosenbaum, *Transmural action potential changes underlying ventricular electrical remodeling.* *J Cardiovasc Electrophysiol*, 2003. **14**(4): p. 394-402.
35. Stambler, B.S., *Tachycardia-induced ventricular electrical remodeling: a perspective on unresolved experimental mechanisms and clinical implications.* *Heart Rhythm*, 2006. **3**(11): p. 1378-81.
36. Spinale, F.G., et al., *Chronic supraventricular tachycardia causes ventricular dysfunction and subendocardial injury in swine.* *Am J Physiol*, 1990. **259**(1 Pt 2): p. H218-29.
37. O'Brien, P.J., et al., *Rapid ventricular pacing of dogs to heart failure: biochemical and physiological studies.* *Can J Physiol Pharmacol*, 1990. **68**(1): p. 34-9.
38. Spinale, F.G., et al., *Changes in myocardial blood flow during development of and recovery from tachycardia-induced cardiomyopathy.* *Circulation*, 1992. **85**(2): p. 717-29.
39. O'Brien, P.J., et al., *Myocardial mRNA content and stability, and enzyme activities of Ca-cycling and aerobic metabolism in canine dilated cardiomyopathies.* *Mol Cell Biochem*, 1995. **142**(2): p. 139-50.
40. Nakamura, R., et al., *Propranolol attenuates left ventricular dysfunction and remodeling in tachycardia-induced heart failure: roles of oxidative stress and inflammation.* *Circulation*, 2002. **106**(3): p. 362-7.
41. Moe, G.W., et al., *How does intermittent pacing modify the response to rapid ventricular pacing in experimental heart failure?* *J Card Fail*, 1995. **1**(3): p. 223-8.
42. Zupan, I., et al., *Tachycardia induced cardiomyopathy in dogs; relation between chronic supraventricular and chronic ventricular tachycardia.* *Int J Cardiol*, 1996. **56**(1): p. 75-81.

43. Umana, E., C.A. Solares, and M.A. Alpert, *Tachycardia-induced cardiomyopathy*. Am J Med, 2003. **114**(1): p. 51-5.
44. Heinz, G., et al., *Improvement in left ventricular systolic function after successful radiofrequency His bundle ablation for drug refractory, chronic atrial fibrillation and recurrent atrial flutter*. Am J Cardiol, 1992. **69**(5): p. 489-92.
45. Packer, D.L., et al., *Tachycardia-induced cardiomyopathy: a reversible form of left ventricular dysfunction*. Am J Cardiol, 1986. **57**(8): p. 563-70.
46. Gopinathannair, R., R. Sullivan, and B. Olshansky, *Tachycardia-mediated cardiomyopathy: recognition and management*. Curr Heart Fail Rep, 2009. **6**(4): p. 257-64.
47. Rodriguez, L.M., et al., *Improvement in left ventricular function by ablation of atrioventricular nodal conduction in selected patients with lone atrial fibrillation*. Am J Cardiol, 1993. **72**(15): p. 1137-41.
48. Williamson, B.D., et al., *Radiofrequency catheter modification of atrioventricular conduction to control the ventricular rate during atrial fibrillation*. N Engl J Med, 1994. **331**(14): p. 910-7.
49. Hsu, L.F., et al., *Catheter ablation for atrial fibrillation in congestive heart failure*. N Engl J Med, 2004. **351**(23): p. 2373-83.
50. Cruz, F.E., et al., *Reversibility of tachycardia-induced cardiomyopathy after cure of incessant supraventricular tachycardia*. J Am Coll Cardiol, 1990. **16**(3): p. 739-44.
51. Chen, S.A., et al., *Reversibility of left ventricular dysfunction after successful catheter ablation of supraventricular reentrant tachycardia*. Am Heart J, 1992. **124**(6): p. 1512-6.
52. Khasnis, A., et al., *Tachycardia-induced cardiomyopathy: a review of literature*. Pacing Clin Electrophysiol, 2005. **28**(7): p. 710-21.
53. Bogun, F., et al., *Radiofrequency ablation of frequent, idiopathic premature ventricular complexes: comparison with a control group without intervention*. Heart Rhythm, 2007. **4**(7): p. 863-7.

54. Takemoto, M., et al., *Radiofrequency catheter ablation of premature ventricular complexes from right ventricular outflow tract improves left ventricular dilation and clinical status in patients without structural heart disease*. J Am Coll Cardiol, 2005. **45**(8): p. 1259-65.
55. Yarlagadda, R.K., et al., *Reversal of cardiomyopathy in patients with repetitive monomorphic ventricular ectopy originating from the right ventricular outflow tract*. Circulation, 2005. **112**(8): p. 1092-7.
56. Baman, T.S., et al., *Relationship between burden of premature ventricular complexes and left ventricular function*. Heart Rhythm. **7**(7): p. 865-9.
57. Fernandez-Sola, J., et al., *Angiotensin-converting enzyme gene polymorphism is associated with vulnerability to alcoholic cardiomyopathy*. Ann Intern Med, 2002. **137**(5 Part 1): p. 321-6.
58. Deshmukh, P.M., et al., *Association of angiotensin converting enzyme gene polymorphism with tachycardia cardiomyopathy*. Int J Mol Med, 2004. **13**(3): p. 455-8.
59. Api, O. and J.S. Carvalho, *Fetal dysrhythmias*. Best Pract Res Clin Obstet Gynaecol, 2008. **22**(1): p. 31-48.
60. Fuster, V., et al., *The natural history of idiopathic dilated cardiomyopathy*. Am J Cardiol, 1981. **47**(3): p. 525-31.
61. Momiyama, Y., H. Mitamura, and M. Kimura, *ECG differentiation of idiopathic dilated cardiomyopathy from coronary artery disease with left ventricular dysfunction*. J Electrocardiol, 1995. **28**(3): p. 231-6.
62. Timek, T.A., et al., *Pathogenesis of mitral regurgitation in tachycardia-induced cardiomyopathy*. Circulation, 2001. **104**(12 Suppl 1): p. I47-53.
63. Paelinck, B., et al., *Usefulness of low-dose dobutamine stress echocardiography in predicting recovery of poor left ventricular function in atrial fibrillation dilated cardiomyopathy*. Am J Cardiol, 1999. **83**(12): p. 1668-71, A7.
64. Malcom, J., et al., *Canadian Cardiovascular Society Consensus Conference guidelines on heart failure--2008 update: best practices for the transition of care of*

- heart failure patients, and the recognition, investigation and treatment of cardiomyopathies. Can J Cardiol, 2008. 24(1): p. 21-40.*
65. Roy, D., et al., *Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med, 2008. 358(25): p. 2667-77.*
 66. Wyse, D.G., et al., *A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med, 2002. 347(23): p. 1825-33.*
 67. Van Gelder, I.C., et al., *A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med, 2002. 347(23): p. 1834-40.*
 68. Opolski, G., et al., *Rate control vs rhythm control in patients with nonvalvular persistent atrial fibrillation: the results of the Polish How to Treat Chronic Atrial Fibrillation (HOT CAFE) Study. Chest, 2004. 126(2): p. 476-86.*
 69. Van Gelder, I.C., et al., *Lenient versus Strict Rate Control in Patients with Atrial Fibrillation. N Engl J Med.*
 70. Prystowsky, E.N., *Assessment of rhythm and rate control in patients with atrial fibrillation. J Cardiovasc Electrophysiol, 2006. 17 Suppl 2: p. S7-10.*
 71. Noe, P., et al., *Rapid recovery of cardiac function after catheter ablation of persistent junctional reciprocating tachycardia in children. Pacing Clin Electrophysiol, 2002. 25(2): p. 191-4.*
 72. Ilkhanoff, L., et al., *Changes in ventricular dimensions and function during recovery of atrial tachycardia-induced cardiomyopathy treated with catheter ablation. J Cardiovasc Electrophysiol, 2007. 18(10): p. 1104-6.*
 73. Tomita, M., et al., *Serial histopathologic myocardial findings in a patient with ectopic atrial tachycardia-induced cardiomyopathy. J Cardiol, 1997. 29(1): p. 37-42.*