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Heart Failure and Sudden Death in Patients With Tachycardia-Induced Cardiomyopathy and Recurrent Tachycardia

Pamela Nerheim, MD; Sally Birger-Botkin, RN; Lubna Piracha, DO; Brian Olshansky, MD

Background—Tachycardia-induced cardiomyopathy is a reversible cause of heart failure. We hypothesized that although left ventricular ejection fraction measurements normalize after heart rate or rhythm control in patients with tachycardia-induced cardiomyopathy, recurrent tachycardia may have abrupt and deleterious consequences.

Methods and Results—Patients with tachycardia-induced cardiomyopathy that developed over years were evaluated and treated. Tachycardia episodes and outcomes were assessed. Twenty-four patients were identified. All had NYHA functional class III heart failure or greater on presentation. One third were heart transplant candidates. There were 17 men and 7 women with a mean age of 46±16 years and mean left ventricular ejection fraction of 0.26±0.09 at the index visit. The cause was atrial fibrillation (n=13), atrial flutter (n=4), atrial tachycardia (n=3), idiopathic ventricular tachycardia (n=1), permanent junctional reciprocating tachycardia (n=2), and bigeminal ventricular premature contractions (n=1). Within 6 months of rate control or correction of the rhythm, left ventricular ejection fraction improved or normalized and symptoms abated in all. Five patients had tachycardia recur. In these patients, left ventricular ejection fraction dropped precipitously and heart failure ensued within 6 months, even though the initial impairment took years. Rate control eliminated heart failure and improved or normalized ejection fraction in 6 months. Three of 24 patients died suddenly and unexpectedly.

Conclusions—Tachycardia-induced cardiomyopathy develops slowly and appears reversible by left ventricular ejection fraction improvement, but recurrent tachycardia causes rapid decline in left ventricular function and development of heart failure. Sudden death is possible. **(*Circulation*. 2004;110:247-252.)**

Key Words: arrhythmia ■ death, sudden ■ heart failure ■ heart rate ■ tachycardia

Tachycardia-induced cardiomyopathy (TIC), a cause of heart failure and impaired left ventricular function, is considered reversible. Left ventricular systolic function, measured by left ventricular ejection fraction (LVEF), improves or normalizes and symptoms resolve if tachycardia is controlled with medication[1,2] or ablation.[3–11] TIC has been described in patients of all ages, in heart transplant patients,[12] and even in utero.[13] Rhythms causing TIC include atrial fibrillation,[14–16] atrial flutter,[17] supraventricular tachycardia,[3,4,8,10,12,18] ventricular tachycardia,[5–7,19,20] fascicular tachycardia,[2] ventricular ectopy,[21] and even persistent rapid DDD pacing.[22] Recurrent tachycardia after apparent resolution of TIC has been described, but the consequences have not been quantified completely.[15]

This report addresses the issue of recurrent tachycardia in patients with prior, apparently resolved, TIC. We hypothesized that although LVEF measurements may improve or normalize after rate or rhythm control in patients with TIC, recurrent tachycardia is associated with rapid development of symptomatic heart failure and a precipitous decline in left ventricular systolic function.

Methods

Study Patients

Patients with heart failure and tachycardia referred to the electrophysiology service were screened. For the patient to be included, no condition other than tachycardia-explained cardiomyopathy and significant improvement in LVEF and symptoms after heart rhythm or rate control was required.

Twenty-four patients (17 men, 7 women) qualified over a 12-year period. The investigators followed up all patients. Their mean age was 46±16 years (range, 22 to 78 years) and mean LVEF was 0.26±0.09 (range, 0.10 to 0.40) at the index visit. LVEF was measured subsequently as indicated. LVEF was evaluated by echocardiography (n=44), radionuclide angiography (n=19), and/or ventriculography during cardiac catheterization (n=3).

Data Collection

The following information was confirmed by chart review after approval from our Institutional Review Board: (1) treatment for TIC, (2) evaluation of symptoms at all follow-up visits, (3) duration of tachycardia before the index assessment for heart failure, (4) time to improvement of LVEF and symptoms, (5) onset of symptoms and impaired LVEF in patients with recurrent tachycardia, and (6) long-term outcome.

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TABLE 1. Clinical Characteristics

Cause	Age, y*	Sex	Time, y	EF Before	EF After	Treatment	Recurrent	Heart Rate, bpm†	Follow-Up, mo
AF	42	M	12	0.17	0.60	Both	Yes	...	81
AF‡	40	M	24	0.10	0.55	Rate	No	120	12
AF‡	28	M	10	0.17	0.48	Both§	Yes	121–150	120
AF	37	M	1	0.28	0.50	Rate	No	...	7
AF	33	F	3.5	0.38	0.50	Both	Yes	56–120	47
AF/AFL	68	M	27	0.20	0.55	Both§	Yes	145	33
AF	45	M	1	0.35	0.48	Both	No	100–150	31
AF	59	M	10	0.27	0.56	Both	No	...	3
AF	70	M	11	0.25	0.50	Rhythm	No	...	40
AF	45	F	1	0.35	0.48	Rhythm	No	...	6
AF‡	42	M	1.5	0.20	0.48	Rhythm	No	...	17
AF	54	M	1	0.20	0.45	Rhythm	No	...	5
AFL/AF	45	M	1	0.38	0.53	Both§	Yes	75–125	8
AF	38	F	1	0.40	0.50	Rhythm	No	...	6
AFL	58	M	2	0.28	0.53	Rhythm§	No	49–295	36
AFL	58	M	10	0.20	0.50	Rhythm§	No	...	6
AFL	75	M	1	0.34	0.50	Rhythm§	No	...	49
AT	28	M	5	0.28	0.50	Rhythm§	No	39–120	1
AT	22	M	2	0.40	0.60	Rhythm	No	112–144	22
AT	78	M	2	0.38	0.48	Rhythm	No	162	3
PJRT	23	F	23	0.20	0.50	Rhythm§	No	110–140	6
PJRT	41	F	30	0.13	0.50	Rhythm§	No	120–132	36
VT	32	F	6	0.15	0.53	Rhythm	No	120–170	52
PVCs	29	F	7	0.30	0.65	Rhythm§	No	...	6
Mean	46±16		8±9	0.26±0.09	0.52±0.05			...	26±29

Cause indicates responsible arrhythmia; AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; PJRT, permanent junctional reciprocating tachycardia; VT, ventricular tachycardia; PVCs, premature ventricular contractions; Age, age at index presentation; Time, time arrhythmia existed before the index visit; EF Before, LVEF before rate or rhythm control; EF After, LVEF after initial rate or rhythm control; Treatment, rate control, rhythm control, or both; and Recurrence, documented tachycardia recurrence.

*Age at presentation to investigator.

†Heart rate measured at index presentation.

‡These subjects died during follow-up.

§AF patients with ablation had ablation of the AV junction.

Statistical Analysis

A Wilcoxon signed-ranks test was used to compare the LVEF obtained at the index visit for initial heart failure symptoms with the LVEF after rate or rhythm correction. Similarly, this test was used to compare the time to symptom onset for the initial episode of tachycardia to the time of symptom onset for the first recurrent episode (for those with recurrence). The Mann-Whitney test was used for between-group comparisons. Exact-distribution tests were used because of sample size.

Results

Initial Presentation

Twenty-four patients had NYHA functional class III or IV heart failure, and 8 were considered heart transplantation candidates when TIC was first suspected (the "index visit" under our care). Despite medical therapy, all patients continued to have heart failure symptoms until tachycardia resolved. Arrhythmia persisted for a median of 4.2 years and a mean of 8.0±9.1 years (range, 1 to 30 years) before heart failure symptoms and impaired LVEF were noted.

Causes and Treatment of TIC

The arrhythmic cause for TIC was atrial fibrillation (n=13), atrial flutter (n=4), atrial tachycardia (n=3), permanent junctional reciprocating tachycardia (n=2), idiopathic ventricular tachycardia (n=1), and bigeminal premature ventricular contractions (n=1) (Table 1). Therapies to control tachycardia included radiofrequency ablation in all patients with atrial flutter, atrial tachycardia, and permanent junctional reciprocating tachycardia and in the patient with bigeminal premature ventricular contractions. Two patients with atrial fibrillation had AV junctional ablation, and 12 required medications. Patients with atrial fibrillation received digoxin, amiodarone, β-blockers, and/or calcium-channel blockers. One patient with atrial fibrillation had supraventricular tachycardia and underwent an unsuccessful right-sided

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TABLE 2. Echocardiographic Dimensions

Cause	LVESD Before, mm	LVEDD Before, mm	LVESD After, mm	LVEDD After, mm
AF*	62	48	...	...
AF*	64	51	...	...
AF	61	50	...	...
AF	58	48	55	35
AF/AFL	57	42	50	37
AFL	63	58	...	...
AT	50	31	41	38
PJRT	...	...	48	33
VT	...	...	58	37
Mean	59	47	50	36

Abbreviations as in Table 1; additionally, LVESD indicates left ventricular end-systolic dimension, and LVEDD, left ventricular end-diastolic dimension.
>*These subjects died during follow-up.

pathway ablation attempt. Another with atrial fibrillation ultimately developed atrial flutter and underwent an atrial flutter ablation procedure.

One patient with an atypical form of idiopathic right ventricular tachycardia had several failed ablation attempts. She was lost to follow-up and took no medication for 8 years. Heart failure ensued, and her LVEF plummeted to 0.15. Suppression of nearly incessant ventricular tachycardia with amiodarone normalized the LVEF and eliminated symptoms.

Ultimately, slowing of the ventricular rate occurred in all patients with treatment. With resolution of tachycardia or with rate control, all patients became asymptomatic, and all LVEFs approached normal.

The mean LVEF before treatment was 0.26±0.09 (range, 0.10 to 0.40). After treatment and with clinical improvement, the mean LVEF was 0.51±0.05 (range, 0.45 to 0.65) (Wilcoxon signed-ranks S=150; n=24; $P<0.0001$). Of the 24 patients, 20 had evaluation of LVEF within 2 years of treatment. The mean time to improvement of the LVEF was 5.8±4.8 months. The time course for symptom resolution mirrored the improvement in LVEF. Echocardiographic dimensions before and after therapy are shown in Table 2.

Recurrent Tachycardia

Rapid Decline in LVEF and Reemergence of Heart Failure

Five of 24 patients had tachycardia recur. In all patients, it was atrial fibrillation (1 also had atrial flutter). Three of these 5 patients had >1 recurrence. LVEF declined and heart failure symptoms developed within 6 months of identification of recurrent tachycardia. This was much faster than the initial decline for each patient: 96±109 months (range, 12 to 360 months) versus 7.2±6.4 months (Wilcoxon signed-ranks test, 2-tailed exact $P=0.0625$).

Example

A 33-year-old woman developed TIC as a result of >8 years of uncontrolled atrial fibrillation. Symptoms resolved and LVEF normalized with treatment. Atrial fibrillation recurred 2 years later, and LVEF dropped precipitously with heart failure symptoms within 6 months. Rate control eliminated symptoms and normalized LVEF within 1 to 3 months. Several months later, after neglecting to take her medication, heart failure symptoms recurred, and LVEF dropped. Symptoms disappeared and LVEF normalized after amiodarone (Figure 1).

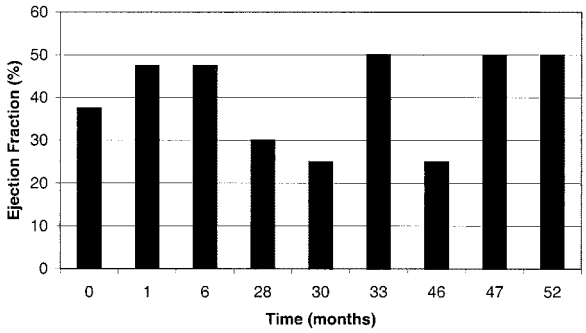

Figure 1. Changes in LVEF in 33-year-old woman with recurrent atrial fibrillation. Cardioverted with Ibutilide, she had recurrence 2 years later (t=24 months). Rate control with metoprolol was unsuccessful. Rhythm control was achieved 4 months later (t=27 months) with amiodarone. At 33 months, her LVEF normalized. At t=43, she stopped amiodarone, and heart failure symptoms developed. Three months later (t=46), her LVEF was 0.25. Amiodarone was restarted. Symptoms disappeared 1 month later, and LVEF normalized.

Sudden Death

An unexpected but important finding was that 3 patients died suddenly. The patients (42, 36, and 44 years of age) had atrial fibrillation that caused cardiomyopathy (Table 3). None had new symptoms, and all had NYHA functional class I heart failure immediately before sudden, unexpected death, according to witnesses. For patients who died, the last measured LVEF approximated 0.50. No patient had evidence of or symptoms related to loss of rate control at the last evaluation.

Cases of Sudden Cardiac Death

Patient 1

A 41-year-old man with untreated atrial fibrillation since he was 15 years of age had persistent tachycardia, developed class III heart failure and syncope, and had an LVEF of 0.10. Amiodarone administration did not maintain sinus rhythm but did slow the ventricular response. Four months later, his LVEF improved to 0.55, and he was asymptomatic. Five months later, amiodarone was stopped, and a β-blocker was started. He died suddenly and unexpectedly 4 months later.

Patient 2

A 26-year-old man had longstanding (>10 years) uncontrolled atrial fibrillation with a heart rate of >195 bpm with

TABLE 3. Characteristics of Patients With Sudden Death

Age, y	Sex	Index LVEF	Last LVEF	Time From Diagnosis to Death
40	Male	0.10	0.55	27 y
28	Male	0.17	0.48	14 y
42	Male	0.20	0.48	18 mo

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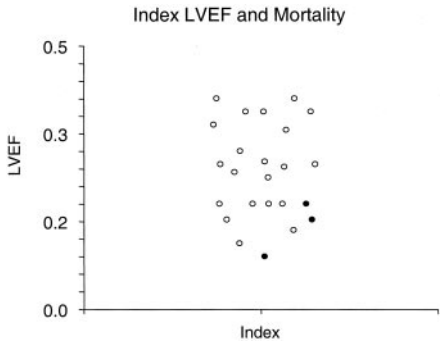

Figure 2. LVEF of those who died vs that of other patients. Index LVEF of those who died was less than that for the others (Mann-Whitney test, exact $P<0.034$). Solid dots represent index LVEF for those who died.

minimal exertion, class III heart failure, and impaired LVEF. Over a 10-year follow-up, he was treated with amiodarone and multiple cardioversions. LVEF improved markedly (and symptoms disappeared) within a month after each cardioversion but dropped precipitously (associated with heart failure) within 4 to 8 weeks after recurrence of rapid rates. Ultimately, he underwent AV junctional ablation and pacemaker implantation. Symptoms resolved, and LVEF was normal for several years. While gardening, he was noted to slump over and die suddenly.

Patient 3

A 44-year-old man had atrial fibrillation for 18 months and noted heart failure symptoms 1 week before his index visit. His LVEF was 0.10, and symptoms did not improve with standard heart failure therapy. Cardioversion 1 month later improved his LVEF to 0.48, and the symptoms resolved. Although atrial fibrillation recurred 6 months later, the rate was controlled. Without symptoms, he died suddenly at home.

The 3 patients who died suddenly had an index LVEF that was significantly less than that of the entire group (Mann-Whitney test, exact $P<0.034$; see Figure 2).

Discussion

TIC is considered a reversible condition on the basis of resolution of symptoms and normalization of the LVEF after the rhythm is corrected or the rate is controlled.[8,15] The heart dilates, LVEF decreases, but hypertrophy does not occur. The time course to recovery has been evaluated. In 8 patients with atrial fibrillation for 10 ± 9 months,[23] LVEF normalized in 1 month.

Similar to previous reports,[2,5–8,10,14–16,22] our data show recovery in the LVEF and resolution of symptoms after treatment. Our report is the first to show that despite apparent resolution of the problem, tachycardia recurrence causes a precipitous decline in LVEF with concomitant symptoms and that there is an association with sudden cardiac death. Our study is the first to quantify the time course of symptom development and the rapidity of impairment of the LVEF with tachycardia recurrence. Other than our report, we know of only 1 other report of 3 patients who had apparent reversible and recurrent tachycardia.[15]

A precipitous drop in the LVEF with tachycardia recurrence suggests persistent ultrastructural changes making the left ventricle susceptible to repeated stress. A permanent change, not measurable by the LVEF or by symptoms, may occur in the left ventricle.

Other data support this finding. Biopsies of 2 young patients with TIC showed mild hypertrophy and focal interstitial fibrosis in 1 patient and mild to moderate cellular hypertrophy with focal degenerative changes and mild to moderate interstitial edema in the other.[1] Persistent ultrastructural changes in animal models suggest other possibilities.

Animal Models

Rapid pacing can initiate cardiomyopathy in animals.[24–28] Eble and Spinale,[29] studying the contractile and cytoskeletal structure in pigs with pacing-induced cardiomyopathy, showed ventricular dilatation without hypertrophy similar to that seen in humans. In a canine model, Kajstura et al[30] found no change in heart weights but observed myocyte replacement with fibrosis. Left ventricular torsional abnormalities[27] and mitral regurgitation[31] occur in sheep. Independent of LVEF measurements, myocyte elongation and misalignment and disruption of basement membrane/sarcolemmal interfaces[32] with developing sarcolemmal festoons[33] and changes in myocyte attachment to laminin, fibronectin, and the extracellular collagen matrix[32,33] may be seen.

Cytoskeletal changes include increased β-actin, γ-actin, and α-tubulin[34]; alteration in matrix metalloproteinases (gelatinase, collagenase, and stromolysin)[35,36]; and depletion of high energy stores. Atrial natriuretic peptide levels, renin-angiotensin, and endothelin activity change.[37]

Downregulation of calcium cycling with lower activity of sarcoplasmic reticulum calcium transport based on ryanodine receptor responsiveness[38] and accumulation[39] occurs. Myofibrillar calcium ATPase activity, sodium-potassium ATPase activity,[40] and cardiac glycoside binding activity[41] are reduced. As part of the remodeling process, epinephrine and norepinephrine levels increase, probably coupled to decreased sympathetic responsiveness and β_1 receptor density.

β-Adrenergic blockers enhance reverse remodeling after myocardial infarction.[42] Data such as these, while compelling, may not apply to TIC because mechanisms for these conditions differ. The LVEF may be a poor surrogate of remodeling; its normalization may not indicate correction of TIC.[43]

In paced animal models of TIC, when pacing is stopped, LVEF normalizes, but hypertrophy develops and diastolic dysfunction persists.[43,44] Because myocardial compliance is reduced and ventricular filling is impeded, high heart rates with recurrent tachycardia may result in shortened filling times and rapidly progressive heart failure.

Any or all of these abnormalities could influence the rate at which LVEF falls with recurrent tachycardia. It is not clear which alteration is the chicken and which is the egg.[45]

Sudden Death: A New Finding

Our report is the first to document risk of sudden death in this population even with apparent rate control. Afonso and

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Franca[46] reported sudden death in a young man with heart failure and supraventricular tachycardia in whom rate control was not achieved. An echocardiogram showed dilated cardiomyopathy. An endomyocardial biopsy showed mild interstitial infiltration.

In a dog model, Pak et al[47] sought to determine whether tachycardia-induced heart failure was an effective model for sudden cardiac death. Six of 25 animals (24%) died suddenly. In 1 dog, a monitor documented polymorphic ventricular tachycardia as the cause of death. Holter recordings revealed increasing ventricular tachycardia episodes as heart failure progressed. The corrected QT interval prolonged significantly (311±25 to 338±25 ms; $P<0.05$), and the monophasic action potential duration (at 90% repolarization) increased from 181±19 to 209±28 ms. Dispersion in monophasic action potential duration rose 40%. Increased cesium chloride sensitivity in myocytes isolated from these failing hearts suggested impaired potassium channel functioning perhaps a precursor to QT prolongation and malignant arrhythmias.

Study Limitations

This study is retrospective, and there was no consistent protocol to measure LVEF. An accurate initial duration of tachycardia and its recurrence were difficult to pinpoint.

Conclusions

TIC initially may take years to develop and may appear to resolve with treatment. Those patients who later develop recurrent tachycardia can have rapid recrudescence of symptoms and a precipitous decline in LVEF. Patients with TIC may have a long-term risk for sudden death. These results suggest that despite improvement with treatment, a surreptitious cardiomyopathy caused by unknown ultrastructural changes may persist. Scrupulous, rapid, and aggressive rate control may prevent serious adverse consequences.

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