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REVIEW ARTICLE

Tachycardia-Induced Cardiomyopathy: A Review of Animal Models and Clinical Studies

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The increasing prevalence of congestive heart failure has focused importance on the search for potentially reversible etiologies of cardiomyopathy. The concept that incessant or chronic tachycardias can lead to ventricular dysfunction that is reversible is supported by both animal models of chronic rapid pacing as well as human studies documenting improvement in ventricular function with tachycardia rate or rhythm control. Sustained rapid pacing in experimental animal models can produce severe biventricular systolic dysfunction. Hemodynamic changes occur as soon as 24 h after rapid pacing, with continued deterioration in ventricular function for up to 3 to 5 weeks, resulting in end-stage heart failure. The recovery from pacing-induced cardiomyopathy demonstrates that the myopathic process associated with rapid heart rates is largely reversible. Within 48 h after termination of pacing, hemodynamic variables approach control levels, and left ventricular ejection fraction shows significant recovery with subsequent normalization after 1 to 2 weeks. In humans, descriptions of reversal of cardiomyopathy with rate or rhythm control of incessant or chronic tachycardias have been reported with atrial tachycardias, accessory pathway reciprocating tachycardias, atrioventricular (AV) node reentry and atrial fibrillation (AF) with rapid ventricular responses. Control of AF rapid ventricular responses has been demonstrated to improve ventricular dysfunction with cardioversion to sinus rhythm, pharmacologic ventricular rate control and AV junction ablation and permanent ventricular pacing. The investigation of potential tachycardia-induced cardiomyopathy in patients with heart failure requires further prospective confirmation in larger numbers of patients, with study of mechanisms, patient groups affected and optimal therapies.

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Congestive heart failure is a major health care problem, affecting 1 to 2 million adults in the United States (1). Hospital admissions for congestive heart failure have more than doubled over the past two decades due to the increased average age of the U.S. population as well as the greater duration of survival of patients with chronic heart disease (2). Given the enormity of this problem, reversible causes of depressed left ventricular systolic function should be vigorously investigated. The effect of tachyarrhythmias on ventricular structure and function is an important area of research because incessant or chronic tachyarrhythmias may cause a tachycardia-induced cardiomyopathy that may be reversible with tachycardia rate or rhythm control. The goal of this review is to summarize 1) the pathophysiologic aspects of pacing-induced heart failure in experimental models; and 2) clinical evidence to support the concept of tachycardia-induced cardiomyopathy.

Animal Models

Experimental tachycardia-induced cardiomyopathy was first described by Whipple et al. (3) in 1962. Although first devised to mimic tachycardia-induced cardiomyopathy in humans, the model has been invaluable to the general study of heart failure by providing a predictable stable model of low output biventricular failure (4–11). Specifically with regard to tachycardia-mediated cardiomyopathy, the model allows study of the effect of chronic rapid pacing on ventricular function, as well as the recovery phase associated with discontinuance of rapid pacing. The progression and reversal of heart failure demonstrate time, rate and species dependency. The dog and pig models are most widely studied and are the basis for this discussion.

Hemodynamic Changes

Sustained rapid atrial or ventricular pacing can produce severe biventricular systolic and diastolic dysfunction in animal models. By pacing at a slower rate or for a shorter duration, a lesser degree of left ventricular dysfunction can be produced (8,12,13). The heart failure is characterized by markedly

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Abbreviations and Acronyms
AF = atrial fibrillation
AV = atrioventricular

elevated ventricular filling pressures (14–16), and severe impairment of left ventricular (up to 55% reduction) and right ventricular systolic function (9,10,16–18). Cardiac output is severely reduced, and systemic vascular resistance is typically elevated (6,7,14,17). Left ventricular systolic wall stress is markedly elevated (12,17,19,20). Moderate mitral regurgitation may develop late in the evolution of heart failure (14). As with other forms of severe heart failure, intense neurohumoral activation is produced with marked elevations of plasma atrial natriuretic peptide, epinephrine, norepinephrine, renin activity and aldosterone (5,21) levels.

The marked ventricular systolic dysfunction results from intrinsic loss of myocardial contractility as assessed by whole-heart and isolated myocyte indexes (15,19,20,22–25). Contractile reserve in response to inotropic agents, volume loading and post-extrasystolic potentiation is diminished or absent (22,25–29). Diminished cardiac sympathetic responsiveness is demonstrable and may be due to a markedly reduced myocyte $beta_1$-receptor density and postreceptor abnormalities of adenylate cyclase and calcium handling (30,31). The data relating to diastolic dysfunction during pacing-induced heart failure are discordant. Multiple studies have demonstrated that whole-heart indexes of diastolic function may be normalized by inotropic agents or correction of loading conditions (24,32,33); however, recent isolated myocyte research has shown primary impairment of intrinsic myocardial relaxation at the cellular level (34).

Cardiac Structural Changes

Chronic rapid pacing produces a markedly dilated cardiomyopathy involving all cardiac chambers. Left ventricular dilation is more marked for end-systolic than end-diastolic volumes (9,17) and produces a spherical chamber geometry (14,15,23). This profound cardiac dilation is typically accompanied by right and left ventricular wall thinning or preservation of wall thickness without either hypertrophy (14,19) or consistent increases in heart weight (7,15,23). However, there are data demonstrating a differential response between the ventricles, with evidence of pacing-induced right ventricular hypertrophy without associated left ventricular hypertrophy (35).

On the cellular level, both myocyte and extracellular matrix remodeling have been documented. With rapid pacing, disruption of both the extracellular matrix architecture and the myocyte basement membrane–sarcolemmal interface occurs (10,22,36–38). The disordered extracellular matrix compromises myocyte alignment, force coupling and transmission and capillary patency, with resultant chamber dilation, wall thinning and contractile dysfunction characteristic of this model (37). Morphologic changes in myocytes themselves that have been reported include myocyte loss, cellular elongation, myofibril misalignment and loss of sarcomere register (10,22,37,38). In a recent study demonstrating chamber dilation and mural thinning in the absence of gross changes in cardiac weight, the cellular basis of remodeling was a 39% loss of myocytes and a 61% increase in volume of remaining myocytes (38). However, the issue regarding myocyte death and hypertrophy remains to be conclusively established because other studies have shown remodeling without evidence of myocyte hypertrophy (39). A shift from myocyte contractile to cytoskeletal protein synthesis has been reported (40).

Time Course and Recovery

After 24 h of rapid pacing, systemic arterial pressure and cardiac output are reduced (7,41). With continued pacing, increasing intracardiac filling and pulmonary artery pressures and decreasing systemic arterial pressures typically plateau at 1 week, whereas cardiac output, ejection fraction and cardiac volumes may continually deteriorate for up to 3 to 5 weeks with development of end-stage heart failure (5,8,14,16).

The recovery from pacing-induced heart failure is a dramatic and unique feature of this model, revealing that the myopathic process associated with rapid heart rates is largely reversible. Within 48 h after termination of pacing, right atrial and mean arterial pressures, cardiac index and systemic vascular resistance approach control levels (12). Left ventricular ejection fraction shows significant recovery by 24 to 48 h and normalizes after 1 to 2 weeks (9,12); however, residual contractile dysfunction is demonstrable in isolated myocytes at 4 weeks of recovery (42). Within 4 weeks, all hemodynamic variables return to control levels; yet end-systolic and end-diastolic volumes remain elevated at 12 weeks after termination of pacing, consistent with extensive ventricular remodeling (8,9,17,23). Diastolic dysfunction remains measurable 4 weeks after pacing (28). Interestingly, left ventricular hypertrophy develops in the 4 weeks after discontinuance of pacing (23,42), possibly owing to either the inability to respond to triggers for hypertrophy during pacing itself or as compensatory remodeling. The demonstrated proliferation of large collagen fiber bundles after termination of pacing may contribute to the left ventricular hypertrophy noted during recovery (37). The ability to modulate the occurrence of ventricular hypertrophy may be an invaluable feature of this model, leading to a better understanding of the factors involved in the development of myocardial hypertrophy.

Mechanisms for Cardiomyopathy

The precise mechanisms responsible for the contractile dysfunction and structural changes of pacing-induced cardiomyopathy are not known. Research to date has focused on 1) myocardial energy depletion and impaired energy utilization; 2) myocardial ischemia; 3) abnormalities of cardiac calcium

regulation; and 4) myocyte and extracellular matrix remodeling. Myocardial energy depletion has been proposed as a possible mechanism for myocardial dysfunction, and studies have demonstrated reduced myocardial energy stores, including creatine, phosphocreatine and adenosine triphosphate; enhanced activity of Krebs cycle oxidative enzymes; mitochondrial structural injury; and mitochondrial functional abnormalities, including diminished mitochondrial cytochrome oxidase staining and creatine kinase activity associated with pacing-induced cardiomyopathy (4,10,18,43,44). However, it is not clear that these findings lead to cardiac dysfunction and may merely be a secondary effect of rapid pacing. Similarly, myocardial ischemia has been a proposed mechanism given supraphysiologic heart rates, reduced systemic arterial pressure and increased ventricular diastolic pressures. Although morphologic and functional abnormalities of the coronary vasculature have been demonstrated, including abnormal subendocardial to subepicardial flow ratios and impaired coronary flow reserves (33,43,45,46), convincing primary roles for either myocardial ischemia or energy depletion have not been established.

The role of abnormal calcium handling in mediating experimental tachycardia-induced cardiomyopathy has received considerable support. Extensive abnormalities of calcium channel activity and sarcoplasmic reticulum calcium transport as assessed by ryanodine receptor response, aequorin light generation and mechanical restitution kinetics may appear within 24 h of pacing and can persist at 4 weeks into recovery (18,26,27,47). These abnormalities in calcium cycling are correlated in severity with the degree of ventricular dysfunction (18). A downregulation of calcium cycling has been documented with lower activity of sarcoplasmic reticulum calcium transport ATPase and myofibrillar calcium ATPase. This downregulation is asymmetric, with the calcium channel being more affected than the calcium pump (18,48). Although derangement in calcium handling is an attractive and potentially unifying mechanism for tachycardia-induced cardiomyopathy, controversy exists as to how abnormalities of calcium regulation may potentially lead to systolic dysfunction. Some groups suggest that systolic dysfunction in pacing-induced cardiomyopathy may be due to decreased calcium sensitivity (27,29), whereas others have shown increased calcium sensitivity and suggest that abnormalities in excitation–contraction coupling may instead be responsible for systolic dysfunction in this model (49). In a recent report, tachycardia-induced cardiomyopathy was found to alter the recovery kinetics of sarcoplasmic reticulum calcium release to a greater extent than calcium sequestration, suggesting that the abnormal time course of calcium availability to myofilaments is the rate-limiting step in recovery of cardiac function (50). Determination of the respective mechanistic roles of calcium handling by the components of the sarcoplasmic reticulum and the contractile apparatus in pacing-induced cardiomyopathy requires further investigation.

Another intriguing proposed mechanism for pacing-induced cardiomyopathy may involve the previously mentioned cellular and extracellular matrix remodeling that occurs with rapid pacing. However, the adaptive or degenerative nature of these morphologic changes remains to be determined.

Human Studies

Historical perspective. Although initial clues that incessant or chronic tachyarrhythmias may lead to reversible ventricular dysfunction date back to the early 1900s, prospective studies of this relation did not begin until the early 1990s. In 1913 Gossage and Braxton Hicks (51) described a case of atrial fibrillation (AF) in a young man who subsequently developed left ventricular dilation and hypertrophy, suggesting that the ventricular dilation and hypertrophy "might very well have been a consequence not a cause of the auricular fibrillation." Reports in the 1930s through the 1940s documented cases of complete resolution of congestive heart failure after cardioversion of AF to sinus rhythm (52–54). Subsequent descriptions of congestive heart failure associated with incessant atrial tachycardia (55–57) and descriptions of reversible cardiomyopathy associated with rate and rhythm control of AF with rapid ventricular responses (58–62), atrial tachycardia (63–70), accessory pathway reciprocating tachycardias (66,67,71,72) and atrioventricular (AV) node reentry (60,73) were reported. Additionally, reversible cardiomyopathy has been reported in the treatment of incessant ventricular tachycardia (64,74).

Atrial fibrillation: restoration of sinus rhythm or ventricular rate control. Because AF is a common arrhythmia in patients with dilated heart failure, investigation of possible tachycardia-induced cardiomyopathy has focused on this population. The effect of control of AF rapid ventricular responses on cardiac function has been preliminarily investigated in small, prospective studies of the following treatment modalities: 1) cardioversion to sinus rhythm; 2) pharmacologic ventricular rate control; and 3) AV junction ablation and permanent ventricular pacing (Table 1).

The study of conversion of AF to sinus rhythm provides information on changes associated with the resumption of atrial contraction and AV synchrony leading to a regularized, rate-controlled ventricular response. Previous studies have documented improvement in cardiac output (75) and cardiopulmonary exercise testing variables of ventricular rate control, maximal oxygen uptake and anaerobic threshold (76,77) after cardioversion to sinus rhythm. More recently, a small, prospective study of patients with a diagnosis of "idiopathic" dilated cardiomyopathy and chronic AF reported a significant increase in left ventricular ejection fraction after pharmacologic or electrical cardioversion to sinus rhythm (78). Whether improvement in cardiac function was due to restoration of atrial systolic function and AV synchrony versus reversal of an underlying cardiomyopathy associated with rapid and irregular ventricular rates during AF was not resolved by this study. Subsequent study of atrial and ventricular systolic function and metabolic exercise testing before and serially after cardioversion in patients with chronic AF with rapid baseline rest ventricular responses demonstrated a dissociation between the early normalization of effective atrial transport (1 day to 1

Table 1. Effect of Atrial Fibrillation Rhythm or Rate Control on Left Ventricular Systolic Function

Study (ref no.)	No. of Pts.	Intervention Type	Method of Assessment	Pre (%)	Post (%)	p Value
Kieny et al. (74)	12	CV	EF	32 ± 5	53 ± 10	< 0.001
Van Gelder et al. (75)	8	CV	EF	36 ± 13	53 ± 8	< 0.05
Twidale et al. (76)	14	AVJ	EF	42 ± 3	47 ± 4	< 0.05
Heinz et al. (77)	10	AVJ	FS	28 ± 9	35 ± 8	< 0.01
Brignole et al. (78)	9*	AVJ	FS	23 ± 5	31 ± 9	< 0.01
	13†	AVJ	FS	40 ± 5	36 ± 6	0.05

*Patients (Pts) with depressed baseline fractional shortening (FS). †Patients with normal baseline fractional shortening. AVJ = atrioventricular junction ablation and permanent pacemaker; CV = cardioversion; EF = ejection fraction; ref = reference.

week) from the much later normalization of left ventricular ejection fraction and peak oxygen consumption (1 month), suggesting that the delayed improvement in cardiac function may be due to reversal of an intrinsic cardiomyopathy associated with AF rather than the contribution of atrial contraction (79).

The effect of heart rate control alone on ventricular function independent of AV synchrony has been studied through the use of AV junction ablation and permanent ventricular pacing. This modality of therapy provides rate control with a regular paced ventricular rhythm. The studies have provided preliminary evidence that benefit can clearly occur without AV synchrony in patients with initial rapid ventricular responses, despite paced rather than spontaneous ventricular activation. In patients with drug-refractory AF or atrial flutter and mildly depressed ventricular function, rate control through radiofrequency energy AV junction ablation and permanent ventricular pacing provided a modest but significant increase in left ventricular ejection fraction without a significant change in treadmill exercise time (80). In a study of patients with AF and ventricular responses >120 beats/min for the majority of the day, left ventricular fractional shortening improved significantly in the patients with baseline depressed fractional shortening and tended toward improvement in patients with normal baseline fractional shortening (81).

In the largest series of 23 patients with AF and rest average ventricular rates >100 beats/min, New York Heart Association functional class decreased significantly, and exercise time increased significantly, with AV junction ablation and permanent ventricular pacing (82). Subgroup analysis demonstrated that in patients with decreased left ventricular systolic function, fractional shortening increased, whereas in subjects with normal baseline left ventricular systolic function, fractional shortening decreased significantly. These findings lead the authors to view treatment of drug-refractory AF patients as a balance between the benefits of rate control versus the possible deleterious hemodynamic effects of right ventricular pacing.

In addition to control of AF rapid ventricular responses, preliminary human data suggest that the irregularity of AF despite "controlled" ventricular rates may contribute to ventricular dysfunction (83–85). A comparison of pharmacologic ventricular rate control versus ventricular rate control plus regularization of rhythm through AV junction ablation and permanent cardiac pacing would help to assess the contribution of irregularity of rhythm to ventricular dysfunction.

Data supporting tachycardia-induced cardiomyopathy have also been provided through assessment of the impact of control of supraventricular tachycardias due to accessory AV pathways and AV node reentrant tachycardia on left ventricular function (67,72,86). In a study of subjects with frequent episodes of tachycardia due to accessory pathways or AV node reentry treated with direct current or radiofrequency energy catheter ablation, there was significant improvement in fractional shortening, nuclear ejection fraction and New York Heart Association functional class (86).

Indirect data that may support the concept that increased heart rate can exacerbate or contribute to left ventricular dysfunction are beta-adrenergic blocking agent trials in chronic heart failure. In these trials, beta-blockers were associated with significant reduction in heart rate and improvement of hemodynamic function and heart failure symptoms (87,88). However, it is unclear from the current data whether the reduction in heart rate contributes to improvement or merely reflects improvement in heart failure caused by other mechanisms.

Limitations. These preliminary human data suggest that supraventricular tachycardias due to rapid ventricular rates and potentially due to irregularity of rhythm may impair left ventricular systolic function in a reversible manner. However, these conclusions are derived from small studies of heterogeneous patient samples using gross measures of left ventricular function. Limitations in some studies include lack of control for rhythm and ventricular rate during comparison of baseline and posttherapy left ventricular function and lack of control for withdrawal of negative inotropic medications. The possible improvement in ventricular function in patients with heart failure and tachycardia rhythm or rate control requires prospective confirmation in larger numbers of patients using currently available treatment modalities and needs to address issues relating to tachycardia-induced cardiomyopathy mechanisms, patient groups affected and optimal therapies. Despite abundant data from animal models of tachycardia-induced cardiomyopathy, there are no significant data on the time course, mechanisms or biochemical changes of tachycardia-induced cardiomyopathy in humans. The relevance of animal models to the human condition has not been established.

Clinical implications. The current published reports focus primarily on patients with a presumed diagnosis of "idiopathic" dilated cardiomyopathy with complete reversibility of ventricular dysfunction with tachycardia rate and rhythm control. Characterization of patients with a "pure" reversible tachycardia-induced cardiomyopathy and differentiation from other patients with dilated cardiomyopathy require investigation. An issue with wider potential ramifications is whether patients with common etiologies of dilated cardiomyopathy may have an additional reversible component of ventricular dysfunction due to tachyarrhythmias. The identification of patient subsets with common etiologies of heart failure who have some reversibility of ventricular dysfunction with rhythm or rate control, as well as the magnitude of their improvement, requires further investigation. Specifically in regard to patients with antiarrhythmic refractory AF and rapid ventricular responses in the setting of depressed ventricular function, controlled clinical trials are necessary to assess which therapeutic modality (pharmacologic or AV junction ablation and permanent pacemaker placement) achieves optimal rate control and optimal systolic function. Because the minimal rate and duration of tachycardia required to induce cardiomyopathy are currently unknown, there could conceivably be a relatively rapid progression to worsening cardiac function in patients with tachyarrhythmias. Until more data are available, heart rate and rhythm control should be rigorously and rapidly pursued if definite signs of a cardiomyopathic process have developed.

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