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Review

Tachycardia mediated cardiomyopathy: Pathophysiology, mechanisms, clinical features and management

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ABSTRACT

Tachycardia mediated cardiomyopathy (TMC) is a reversible form of dilated cardiomyopathy that can occur with most supraventricular and ventricular arrhythmias. Despite the plethora of literature describing this entity in animal models, as well as humans, it remains poorly understood. Over the last decade, new etiologies of TMC, such as frequent premature ventricular complexes in normal hearts, have been identified. Recent advances in catheter-based ablation therapies, particularly for atrial fibrillation and ventricular arrhythmias, have added a new dimension to the treatment of this condition. This review describes the pathophysiology, proposed mechanisms, clinical features and management in various arrhythmic conditions.

1. Introduction

Incessant tachyarrhythmias can lead to ventricular dilation and systolic dysfunction with signs and symptoms of heart failure (HF). Tachycardia-induced HF was first described in 1913 in a patient with atrial fibrillation [1]. Philips and Levine described the relationship between rapid atrial fibrillation and reversible heart failure in 1949 [2]. Whipple and colleagues developed an experimental model of tachycardia-mediated cardiomyopathy (TMC) in 1962 [3]. Fenelon and colleagues divided TMC in to two types: 1. pure, where tachycardia is the sole mechanism of worsening of LV function; and 2. impure, where tachycardia worsens a pre-existing cardiomyopathy due to a different cause [4].

Over the last 3 decades, multiple papers have described this entity in both animal models and in humans. Despite the plethora of literature, TMC remains a poorly understood entity. This review describes the pathophysiology, clinical features and natural history of TMC.

2. Pathophysiology and proposed mechanisms

2.1. Systolic function

In animal models of pacing-induced HF, sustained atrial or ventricular pacing produce severe biventricular systolic dysfunction. This is characterized by increased ventricular filling pressures, decreased cardiac output and increased systemic vascular resistance, without a change in left ventricular (LV) mass [5–7]. There is loss of intrinsic myocardial contractility with diminished contractile reserve. The marked dilation of ventricles is accompanied by lack of hypertrophy of the left ventricular wall. Microscopic alterations include myocyte loss, myocyte elongation, and effacement of the interface between the basement membrane and sarcolemmal surface. The latter leads to decrease force transmission through the ventricular wall [8,9]. Depletion of T-tubules occurs in failing ventricular myocytes with rapid pacing, with associated decreases in the density of L-type calcium channels and beta-adrenergic receptors in both surface and T-tubular sarcolemmata. This heterogeneous loss of T-tubules results in abnormal excitation–contraction coupling and may impair contractile efficiency by causing variability in time course of activation of cells [10].

2.2. Diastolic function

Tachycardia also affects diastolic function by causing incomplete relaxation whereby the myocardium remains in a constant activated state that can be described as a partial or diastolic contracture [11]. Calcium extrusion from cardiomyocytes occurs mainly by the sarcolemmal sodium–calcium exchanger. In concert with the sarcoplasmic reticulum (SR), the exchanger restores cytosolic calcium to diastolic levels, thereby causing relaxation. With tachycardia, there is a disproportionate increase in SR calcium content, causing extrusion of calcium in a high calcium environment, which manifests as diastolic contracture [12].

2.3. High energy phosphates

TMC causes depletion of high energy stores in the myocardium due to increased metabolism from persistent tachycardia; this being a

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reversible process. Tissue adenosine triphosphate (ATP), as well as sodium–potassium ATPase, are significantly decreased in animals with pacing-induced HF [13,14], while there is an increase in beta-oxidation enzymes and enzymes involved in the Krebs' cycle [15]. Selective endothelin-receptor blockade has been shown to attenuate progression of HF by reversing mitochondrial dysfunction (specifically by affecting levels of respiratory complexes V and III involved in the Krebs' cycle) in animal models of TMC, thus suggesting the role of endothelin activation in causing ventricular dysfunction [16].

2.4. Myocardial blood flow

Chronic supraventricular tachycardia (SVT) in animals has also been shown to result in decreased myocardial blood flow, which normalizes after pacing is terminated [17,18]. This may be due to marked elevation of LV end-diastolic pressure [19].

2.5. Oxidative stress

Oxidative stress has been proposed as a mechanism contributing to TMC in patients with atrial fibrillation (AF). In AF, oxidative modification of ventricular myofibrillar proteins occurs due to peroxynitrite formation, leading to loss of fibrillar function, eventually causing contractile dysfunction [20,21]. In an animal study of pacing-induced HF, antioxidant vitamins reduced myocardial oxidative stress, attenuated cardiac dysfunction and prevented myocardial beta-receptor down-regulation and sympathetic nerve terminal dysfunction [22].

2.6. Angiotensin converting enzyme

Angiotensin-converting enzyme (ACE) polymorphisms have also been implicated in TMC. Patients with DD genotype (287 base pair deletion in intron 16 of the ACE gene) show exaggerated ACE production in response to any stimulus such as incessant tachycardia. The resultant increase in levels of angiotensin-II causes myocyte elongation, left ventricular enlargement and changes in wall stress [23,24].

2.7. Neurohormonal changes

The neurohumoral changes seen in TMC are similar to those in other forms of HF and occur in response to a depressed cardiac output. Activation of the renin–angiotensin–aldosterone axis occurs with elevated levels of angiotensin-II, atrial natriuretic peptide (ANP) and endothelin-1, causing abnormal sodium handling. In pacing-induced HF, changes in heart rate, atrial pressure and volume cause increased plasma ANP concentrations, which are attenuated by 1 week due to inability of the atria to be stretched further and because of depletion of atrial ANP concentrations [25,26]. As in other disease states, elevated levels of aldosterone may lead to myocardial fibrosis [27,28].

2.8. Beta-adrenergic receptors

There is blunted response to beta-adrenergic stimulation in TMC due to decreased expression of beta-receptors, alterations in beta-receptor transduction including decreased G stimulator protein density (Gs), increased G inhibitory protein density (Gi), and reduced adenylate cyclase activity [29–31].

2.9. Mitral regurgitation

Similar to other forms of dilated cardiomyopathy, patients with TMC can develop mitral regurgitation (MR) due to mitral annular dilatation and separation of the leaflet hinge points, causing incomplete leaflet coaptation and valve incompetence [32]. The saddle shaped mitral annulus in TMC dilates more in the septal–lateral than in the commissure–commissure dimension with flattening of the annulus and decreased contraction occurring in the lateral annulus [33]. There is also lengthening of the mitral leaflets due to remodeling near the leaflet edges [34].

2.10. Right ventricle

The right ventricle (RV) responds somewhat differently to tachycardia. Unlike the LV where chamber dilation occurs without increase in mass, in the RV, both chamber and myocyte hypertrophy develop. These changes in RV myocardial geometry are associated with persistently higher RV myocyte contractile function compared to LV myocytes in TMC [35].

2.11. Recovery from TMC

In animal studies, recovery from TMC is associated with a hypertrophic response of the left ventricle with persistent dilation despite normalization of systolic function [17]. This has subsequently been confirmed in clinical studies [36]. Diastolic dysfunction can persist even after normalization of systolic function [37]. Myocardial blood flow returns to normal, but with decreased coronary flow reserve. Therefore, episodic increases in myocardial oxygen demand in post-supraventricular tachycardia hearts (e.g., with recurrence of tachycardia) can result in reduced myocardial blood flow and reduced LV function [17].

In a study comparing patients with TMC due to SVT with those with idiopathic dilated cardiomyopathy (DCMP), significant improvement in LV ejection fraction was noted in the former group with rate control. LV dimensions and mass and volume indices were smaller in the TMC group than DCMP group. A lower LV end-diastolic dimension was the only significant predictor of recovery in multivariable analysis [38].

In a recent study of 18 patients with TMC due to focal atrial tachycardia that had an improvement in ejection fraction within 3 months of radiofrequency ablation, subtle differences in LV structure and function were noted at 5 years, with larger LV dimensions, lower EF, decreased myocardial strain and twist rate and evidence of diffuse myocardial fibrosis on late gadolinium enhanced cardiac MRI, suggesting incomplete recovery [39].

3. Tachycardia-mediated atrial cardiomyopathy (TMAC)

Atrial tachycardia and atrial fibrillation (AF) have been shown to cause contractile dysfunction of the atria. In addition, cardioversion of AF to sinus rhythm causes atrial mechanical dysfunction, the degree of which depends upon the duration of preceding AF [40,41]. Rapid atrial pacing affects both atrial systolic and diastolic function characterized by absent atrial booster pump function, increased atrial chamber stiffness, enhanced atrial conduit function, and atrial enlargement [42]. Abnormalities in calcium handling and impaired systolic transient calcium currents due to downregulation or dysfunction of the L-type calcium channel and altered myofilament function (associated with abnormal myosin and myosin-associated protein phosphorylation) have been proposed as mechanisms of the atrial cardiomyopathy [43–46]. Upregulation of the sodium–calcium exchanger worsens calcium depletion by causing its efflux from atrial cardiomyocytes of AF patients, thus contributing to the atrial contractile dysfunction post cardioversion. Unlike its ventricular counterpart, beta-adrenergic receptor desentization does not contribute to TMAC [47].

4. Incidence and predisposing factors

The incidence of TCM is variable depending upon the type of tachycardia. In a study of 625 patients referred for radiofrequency ablation of tachyarrhythmias, TCM was found in 17 patients (2.7%) [48]. The incidence for specific arrhythmias has been described as ranging from 10% in patients with focal atrial tachycardia [49], to 20–50% in patients with permanent junctional reciprocating tachycardia (PJRT) [50,51]