The Egg Came First: Arrhythmia Induced Cardiomyopathy

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Cardiologist Richard Wu, M.D. is a nationally recognized expert in evaluating and treating heart rhythm disorders and has been at the forefront of performing cardiac ablation procedures to treat these conditions for over 20 years. Dr. Wu earned both his undergraduate and medical degrees with honors at Duke University. As a Sarnoff Cardiovascular Research Foundation Fellow and Scholar, he was encouraged to pursue an academic career in the field of cardiology. He completed his training in internal medicine, cardiology and cardiac electrophysiology at the Johns Hopkins Hospital. He was inspired by his mentors to specialize in the new developing field of catheter ablation, a minimally invasive method for eliminating fast heart rhythms. His first faculty position was the University of Oklahoma, where he worked with pioneers in the development of 3D mapping and ablation of complex arrhythmias. Dr. Wu joined the faculty at the University of Texas Southwestern Medical Center at Dallas in 2006, where he now serves as Professor of Internal Medicine and is the Director of the Electrophysiology Lab at Clements University Hospital. Dr. Wu has a particular interest in catheter ablation of atrial fibrillation, ventricular tachycardia, and arrhythmias in patients with accessory atrioventricular pathways (Wolff-Parkinson-White syndrome). In addition to helping patients, Dr. Wu enjoys his role mentoring young physicians in training and teaching them innovations in his specialty.

Overview

1. Arrhythmia induced cardiomyopathy (AIC) is a form of heart failure induced by atrial or ventricular arrhythmias.
    a. Tachycardia mediated-cardiomyopathy (rapid heart rhythms)
    b. Premature ventricular contractions (PVC)-induced cardiomyopathy
2. A common clinical problem is determining whether AIC is the primary cause of cardiomyopathy or if it is secondary to cardiomyopathy of a different etiology
3. A hallmark of AIC is partial or complete reversibility of ventricular dysfunction once the arrhythmia is eliminated or controlled
4. Early recognition and prompt treatment of AIC may normalize heart function, prevent further development of heart failure, and prevent sudden cardiac death.

Educational Objectives

1. Identify patients at risk of developing arrhythmia induced cardiomyopathy (AIC)
2. Describe approaches or methods for diagnosing AIC
3. Understand treatment options for treating AIC.

Introduction

Arrhythmia induced cardiomyopathy (AIC) is a condition associated with either atrial or ventricular tachycardia (tachycardia-mediated cardiomyopathy) or frequent premature ventricular contractions (PVC induced cardiomyopathy) leading to systolic heart failure.[1, 2] A hallmark of AIC is partial or complete reversibility once arrhythmia control is achieved. Since the prevalence of arrhythmia in heart failure is high, it may be difficult to determine if the arrhythmia is the primary cause. AIC may be classified as arrhythmia-induced (primary reason for ventricular dysfunction) or arrhythmia-mediated (contributes to worsening of ventricular function in patient with concomitant structural heart disease).

Case reports of ventricular impairment associated with chronic atrial fibrillation were reported in the early 20th century. Back then, there was debate about which came first, chicken or egg: ventricular dysfunction from organic heart disease such as myocarditis or chamber dilation from uncontrolled tachycardia. In 1949, Phillips and Levine described a cohort of patients with atrial fibrillation and rapid ventricular rates that developed progressive ventricular dilation without other evidence of organic heart disease. A potentially reversible form of heart failure was observed in patients who returned to normal sinus rhythm during treatment with the anti-arrhythmic drug quinidine.[3]

The concept of PVC-induced cardiomyopathy was proposed in the late 1990's by Duffee and colleagues, who observed a small group of patients with presumed idiopathic dilated cardiomyopathy recover after suppression of frequent PVC's with pharmacological therapy including treatment with amiodarone.[4]

The advent of cardiac catheterization, surgical and catheter ablation, and histologic analysis of biopsy specimens in later years has allowed differentiation between AIC and primary cardiomyopathy.[5-7] Thus the chicken-egg dilemma was resolved by demonstration of partial or complete reversal of ventricular dysfunction after ablative treatment of the causative arrhythmia in patients with otherwise structurally normal hearts.[8, 9]

Epidemiology

The exact incidence of AIC remains uncertain since overlap between arrhythmia and cardiomyopathy may develop over years. Atrial fibrillation (AF) is the most common cause of AIC in adults. AF has a high prevalence (1% in adults, 5% in adults over age 65) and the diagnosis of AF in patients with a history of heart failure is approximately 25%.[2, 10] In a large contemporary cohort study of patients referred for catheter ablation of tachy-arrhythmias, the incidence of AIC was 2.7%.[11] However, the incidence may be higher for specific arrhythmias, between 10-30% in patients with persistent focal atrial tachycardia or atrial flutter.[1]

Frequent idiopathic premature ventricular contractions (PVC's) have been more recently recognized as a cause AIC. The most significant predictor of cardiomyopathy in patients with PVCs is a high arrhythmia burden ranging from >10,000 to 25,000 PVC/day (or between > 10 to 25% of the total heart beats/day).[12, 13] The prevalence of "frequent" PVCs (>60 beats/hours) is between 1-4% in the general population; however, the proportion of individuals with a very high burden PVCs (>10% total beats) without structural heart disease is low ~1/1000.[14, 15] The incidence of AIC ranges between 9 to 34% in patients with frequent premature ventricular complexes (PVCs) referred for electrophysiological evaluation.[1, 16]

Pathophysiology

Tachycardia-Induced Cardiomyopathy in Animal Models

Chronic tachycardia or high heart rates (>100 bpm) of sustained duration is associated with structural changes including left ventricular dilation, systolic dysfunction and cellular remodeling. Animal models have been developed which show time-dependent development and progression of cardiomyopathy with rapid ventricular pacing. Within 1 to 7 days, left ventricular (LV) dilation, wall thinning, and decline in LV systolic function is seen. However, in the first week, cardiac output and systemic pressures are generally maintained. By the second week, both central and pulmonary venous pressures increase and systemic vascular resistance develops followed by eventual low-output heart failure. After 1 month of pacing, LVEF may drop from normal ejection fraction (EF 55%) to severely depressed (<15%). When pacing is discontinued to allow resumption of sinus rhythm, recovery can be dramatic with left and right filling pressures returning to normal control levels and EF doubling within 48 hours. However, residual contractile dysfunction and dilation of the left ventricle persists consistent with structural remodeling.[17] Recovery of LVEF to normal levels is seen after 1 to 2 weeks.[10] End-systolic and end-diastolic volumes remain elevated at 12 weeks and diastolic dysfunction may remain. Myocardial histology shows reduced myocardial energy stores, absence of cardiac hypertrophy, and changes that are not due to myocardial ischemia.[18] When animals are rapidly paced intermittently (48 hours pacing alternating with 24 hours sinus rhythm for 7 weeks), physiologic changes are seen but not to the same extent.[10]

On a cellular level, the extracellular matrix becomes disordered, myocytes are elongated, myofibrils misalign and some myocytes are lost. The cardiac sympathetic system shows reduced myocyte beta-receptor density, post receptor abnormalities of adenylate cyclase and calcium handling. Derangements in calcium handling are seen such that derangements in the recovery kinetics of sarcoplasmic reticulum calcium release and sequestration lead to systolic dysfunction.[10]

Irregular rhythm and Dyssynchrony

PVC induced cardiomyopathy can be due to tachycardia but a normal heart rate is commonly seen. The possible causes likely include a combination of an irregular

rhythm causing dispersion of contractility and eccentric activation causing radial strain in the ventricle, both producing abnormal regional mechanical function. PVC burden > 24% is independently associated with PVC induced cardiomyopathy.[19] Longer coupling intervals and greater dispersion are associated with PVC cardiomyopathy.[20] Dyssychrony is greater in animal models when PVCs are delivered in longer coupling intervals (400ms vs 200ms). In short-coupled PVCs, maximum contraction occurs in the same segment. However, longer coupled PVCs intervals cause dyskinesis such that contraction in one segment of the heart, e.g., the septum, may be occurring while the opposite segment, the free wall, is contracting.[20]

No inflammation, fibrosis or changes in apoptosis and mitochondrial oxidative phosphorylation were seen in pacing induced PVC cardiomyopathy.

Clinical Features and Time Course

Clinical presentation of AIC is variable. Patients may present with symptoms of palpitations or those more consistent with heart failure (shortness of breath, chest discomfort, edema, or fatigue). However, patients may initially have mild or minimal symptoms for weeks, months or years.[1] Some investigators have hypothesized that AIC patients who present with tachycardia-induced cardiomyopathy have relatively slower rates between 100-120 bpm, since patients with rapid ventricular rates > 150 bpm tend to develop acute symptoms and seek medical attention before significant LV remodeling occurs. These findings are supported by cohort studies examining patients referred for ablation of focal atrial tachycardia.[21, 22]

A small case series that followed patients admitted for new onset congestive heart failure attributed to TCM with average heart rate 150 bpm found that the mean period between the occurrence of tachy-arrhythmias (AF, flutter, AVNRT, idiopathic VT) and the development of CHF was 26.0$\pm$34.3 days. Average LVEF was 32% at time of diagnosis. After treatment with either beta blocker or ablation (no class I or III anti-arrhythmic drugs), all patients had improvement of symptoms from NYHA class II-III to class 1, and recovered normal LVEF during a mean 53.5 days.[23]

Another small case series of CHF patients with chronic atrial fibrillation on rate or rhythm control developed tachycardia-induced cardiomyopathy (TCM) over a longer period of time, mean 96 months (range 12-360 mo). All patients recovered normalized LVEF with treatment but ~25% received a recurrent diagnosis of TCM, generally after stopping an anti-arrhythmic drug such as amiodarone, and LVEF declined more rapidly within 6 months.

For patients with frequent PVCs, signs may include history of low or irregular pulse rate due to bigeminal rhythm, which can cause an alternating strong and weak pulse. About a third of patients with PVC-induced cardiomyopathy have minimal symptoms, whereas ~70% report some palpitations, 50% have fatigue, and 30% report history of [near] syncope.[20, 24]

Development of PVC-induced cardiomyopathy is more insidious. A study from Japan followed asymptomatic individuals without structural heart disease newly diagnosed with PVCs over a course of 4 years and prescribed only beta-blockers. During follow-up, patients with high PVC burden >20,000 beats/day demonstrated progressive decline in LV systolic function and exhibited LV dilation.[12]

Differential Diagnosis

The possibility of AIC should be considered in any patient with a new diagnosis of systolic heart failure and global LV dysfunction. Patients may not present with an arrhythmia or have abnormality on their initial ECG.[1]

The key diagnostic feature of AIC is the presence of either sustained uncontrolled tachycardia or persistent arrhythmia, such as frequent ventricular ectopy, which results in left ventricular dysfunction or otherwise unexplained cardiomyopathy.[1, 5, 16, 25]

Arrhythmias associated with AIC:

Supraventricular	Ventricular
Atrial fibrillation	Premature Ventricular Complexes
Atrial flutter	RV outflow tract ventricular tachycardia
Atrial tachycardia	Idiopathic Ventricular Tachycardia
AV nodal reentrant tachycardia	Fascicular Ventricular Tachycardia
AV reentrant tachycardia	Papillary Muscle PVCs or VT
Pulmonary vein tachycardia	Epicardial PVCs or VT
Permanent Junctional Reciprocating Tachycardia	

Patients should have no evidence of significant coronary artery disease or valvular heart disease. Other Reversible Dilated Cardiomyopathies that should be excluded:

Alcohol or Drug-induced cardiomyopathy

Inflammatory or Infectious myocarditis

Thyroid Disease-Induced Cardiomyopathy

Diagnostic Testing

Cardiac ECG monitoring: heart rate should be measured over >24 hours, with using ambulatory (Holter) ECG monitor or inpatient telemetry to document average heart rate. Extending ECG monitoring or several 24 hour Holters may be warranted since a single recording may not reflect true arrhythmia burden. Frequent, sustained heart rates > 100

bpm and tachycardia during sleep are findings seen in tachycardia-mediated cardiomyopathy.[1, 10]

As discussed earlier, high PVC burden >10,000 beats/day or >10% total beats is associated with PVC-induced cardiomyopathy.[7, 13]

Cardiac imaging and Assessment of Cardiac Structure and Function

All patients with suspected AIC should undergo assessment to document left ventricular size, function and left ventricular ejection fraction (LVEF).

Echocardiogram is the most common non-invasive imaging test for evaluating LV size and function. A small study comparing tachycardia-mediated cardiomyopathy (TMC) patients to idiopathic dilated cardiomyopathy (DCM) suggests initial LV end-diastolic dimension≤61mm and absence of hypertrophy helps differentiate AIC from DCM. In the TMC group, average EF increased from 30% range to 58 after treatment. With no change in DCM.[26]

Cardiac magnetic resonance (CMR) imaging, particularly late gadolinium contrast-enhanced (LGE) imaging is considered a predictor of adverse outcomes in non-ischemic cardiomyopathy.[27] Presence of LGE correlates with fibrosis or scar. In patients diagnosed with presumptive AIC due to PVCs or ventricular tachycardia, LGE may be used to confirm diagnosis since it should be a rare finding (<5%).[28, 29]

Cardiac Catheterization

Coronary angiography, combined left and right heart catheterization, and endomyocardial heart biopsy may be performed to exclude coronary artery disease, myocarditis, or other primary causes of cardiomyopathy.[1, 16, 30] This may also be performed if suspected AIC recurs.

Invasive Electrophysiology Study

For patients with suspected PVC-induced cardiomyopathy referred for PVC ablation, invasive programmed stimulation at time of the procedure may identify patients at higher risk for sustained ventricular tachycardia requiring implant of an ICD for secondary prevention of sudden cardiac death, however it should be a rare finding (<5%).[31]

Treatment

Tachycardia-Mediated Cardiomyopathy

For patients with atrial fibrillation or flutter, prevention of thromboembolism with an anticoagulant is recommended since patients with AIC will have CHA2DS2-VASc ≥1 with systolic heart failure. Rate control using a beta blocker or non-dihydropyridine calcium channel antagonist is recommended.[30] An attempt at cardioversion is recommended to restore sinus rhythm when AF contributes to ongoing heart failure.[30]

Amiodarone or even AV nodal ablation with permanent pacemaker may be performed when pharmacological therapy is inadequate or rhythm control is not achievable.[30]

Controversy exist whether restoration of sinus rhythm or rhythm control is superior to rate control in patients with AIC. Older atrial fibrillation trials comparing rate vs rhythm control such as AFFIRM did not specifically study patients with systolic heart failure; and the AF-CHF trial excluded patients with suspected AIC or "reversible cause of heart failure." Anti-arrhythmic drugs used for patients with AIC and heart failure include amiodarone, sotalol and dofetilide.[30] Amiodarone appears safe and effective in patients with heart failure but is associated with increased risk of symptomatic bradycardia requiring implant of a pacemaker. Dofetilide is associated with reduced hospitalizations for heart failure but cannot be used in patients with severe renal failure or prolonged QT intervals. Catheter ablation of AF (pulmonary vein isolation) has been shown to be effective in patients with systolic heart failure and my result in significant improvement to LVEF compared to drugs.[32-34] Restoration of sinus rhythm by pulmonary vein isolation has been shown to be superior to AV node ablation combined with bi-ventricular pacing for improving mean LVEF, exercise capacity and symptoms.[33]

PVC-mediated Cardiomyopathy

In the presence of reduced left ventricular function, a trial of a beta blocker (metoprolol succinate or carvedilol) is considered first-line therapy for PVC-mediated cardiomyopathy.[16] Anti-arrhythmic drugs such as amiodarone are considered reasonable. Catheter ablation is recommended for patients with frequent PVCs (generally >15% beats and predominately of 1 morphology) who fail, cannot tolerate or prefer to avoid chronic anti-arrhythmic drug therapy.[16]

Prognosis

Tachycardia-Mediated Cardiomyopathy

In tachycardia-mediated cardiomyopathy (TMC), conversion to sinus rhythm or control of ventricular rate is considered to have a good prognosis, particularly in younger patients with successful surgical or catheter ablation of incessant supraventricular tachycardias.[1, 21] In studies examining TMC due to multiple mechanism of arrhythmias, the average initial LVEF is generally between 30-35% and normalized to low normal LVEF ~ 55% with treatment.[1, 10] Persistent atrial fibrillation is the most studied arrhythmia associated with TMC and LV function generally improves with rate or rhythm control. However, more recent studies suggest patients with chronic systolic heart failure and reduced LVEF<40% experience greater improvements in systolic function, hospitalization rates, quality of life and perhaps mortality when sinus rhythm is restored by catheter ablation compared to standard medical therapy.[35]

In two studies examining long-term outcomes, recurrence of TCM was seen in ~25%, particularly in atrial fibrillation or flutter patients with inadequate rate control or after discontinuation of amiodarone (none were treated with contemporary AF ablation techniques).[2, 23] Sudden death occurred despite initial recovery of systolic function in a very small number of patients, and this was characterized by a either lower LVEF<20% at time of index diagnosis of TCM-CMP or an atypically prolonged interval (> 6mo) to recover LV function after initiation of treatment .[2, 23]

PVC-mediated Cardiomyopathy

In a study comparing examining efficacy of anti-arrhythmic drugs and catheter ablation for the treatment of frequent PVC, the efficacy of beta-blocker was 36% compared to 82% for those treated with anti-arrhythmic drugs including amiodarone and mexiletine.[36] Over 15 studies have examined the efficacy of catheter ablation for idiopathic PVCs including those with PVC induced cardiomyopathy (between 20-30% pts referred for PVC ablation) and long-term success rate, which includes some patients with multiple ablation procedures or concomitant use of anti-arrhythmic drugs, is approximately 75%. Overall, baseline LVEF 40% improved to 50% after ablation.[37, 38]

Conclusion

Arrhythmia-induced cardiomyopathy (AIC) is a form of heart failure associated with chronic tachycardia or frequent premature ventricular contractions. Early recognition and proper treatment are essential because AIC is potentially reversible and systolic function may normalize following therapy to control ventricular rate or restore normal sinus rhythm. The clinical presentation is variable, and patients may report symptoms associated with heart failure rather than palpitations. On initial presentation, distinguishing AIC from dilated cardiomyopathy with secondary arrhythmias can be challenging. The use of ECG monitoring to detect high arrhythmia burden and cardiac imaging to evaluate for structural heart disease are required. Persistent atrial fibrillation is the most common cause of AIC in adults, and management often requires a combination of rate or rhythm control in addition to guideline directed medical therapy. PVC-induced cardiomyopathy is a less common cause of AIC, and may take years to develop. Despite absence of symptoms, treatment of individuals with a high burden of PVCs > 10,000 beats/day may prevent development of left ventricular dilation and systolic heart failure. Newer studies suggest restoring or maintaining sinus rhythm in patients with either persistent atrial fibrillation or frequent PVCs with heart failure with catheter ablation may offer better clinical outcomes compared to medical therapy alone. Patients with history of AIC may not have complete normalization of ventricular structure or function as previously believed and are at risk for more rapid clinical deterioration with recurrent arrhythmias. Recognition of arrhythmia-induced cardiomyopathy along with aggressive management, and continued surveillance of individuals with a history of AIC may ultimately improve long-term outcomes for these patients.

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