Review Article

Arrhythmia-Induced Cardiomyopathy

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Abstract
Tachycardia is one of the important reversible causes of ventricular dysfunction. More recently, it has been recognized that premature ventricular complexes and atrial fibrillation can result in or contribute to ventricular dysfunction in the absence of a rapid ventricular rate. The term arrhythmia-induced cardiomyopathy was introduced to include all these potential causes. In this review, we will discuss our understanding of AiCMP and current best practices for its diagnosis and management.

Keywords
Arrhythmia-induced cardiomyopathy, tachycardia-induced cardiomyopathy, ventricular dysfunction, premature ventricular complexes, atrial fibrillation

Received 11 December 2020; accepted 23 December 2020

Introduction
Cardiomyopathies are a group of diseases that affect heart muscle and, in the phenotype of dilated cardiomyopathy, result in ventricular enlargement and reduced ejection fraction. Reversible causes are important because idiopathic dilated cardiomyopathy has a bad long-term prognosis. Arrhythmia-induced cardiomyopathy (AiCMP) is one of the important reversible causes where a cardiac arrhythmia results in or contributes to the ventricular dysfunction so that control of the arrhythmia can completely or partially reverse the cardiomyopathy. In this review, we will discuss our understanding of AiCMP as it has evolved over time and also the current best practices for diagnosis and management of these patients.

History and Terminology
Tachycardia-induced cardiomyopathy (T-CMP) was first described by Gossage et al¹ in 1913 in a patient with atrial fibrillation (AF) with rapid ventricular response. Subsequently, the development of reversible heart failure (HF) with rapid pacing was demonstrated in an animal model.² The term T-CMP was then used to denote the development of ventricular dysfunction due to rapid ventricular rate irrespective of type of tachycardia.

Over the last few decades, it was recognized that frequent premature ventricular complexes (PVCs) could cause ventricular dysfunction.³,⁴ Although these patients were initially labeled as T-CMP, they did not have sustained tachycardia and different mechanisms were likely responsible for the ventricular dysfunction. So, the term PVC-induced cardiomyopathy was used for this condition.

Similarly, it was recognized that although AF can result in T-CMP due to a rapid ventricular rate, ventricular dysfunction could also be seen in patients with AF who had a controlled ventricular rate. Thus, the term AF-induced cardiomyopathy was used to describe these patients.⁵

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Since various arrhythmias can result in the development of reversible ventricular dysfunction with the mechanism not limited to tachycardia alone, the broader term “AiCMP” was introduced and is favored now. This term includes tachycardia, frequent PVCs, and AF as a cause for CMP. The defining characteristic of AiCMP is presence of ventricular dysfunction in a patient with an arrhythmia and its partial or complete recovery once the arrhythmia is effectively suppressed. AiCMP does not include conduction abnormalities induced ventricular dysfunction such as left bundle branch block, preexcitation, and chronic right ventricular pacing.

Of note, arrhythmias not only can induce ventricular dysfunction and HF in a normal heart but can also worsen ventricular function in a person with structural heart disease. Effective suppression of arrhythmia in such cases leads to improvement, but not normalization of ventricular function.

Epidemiology

Incidence and prevalence of arrhythmia-induced CMP is not clear and, on the whole, it appears to be an underrecognized condition. Many different forms of tachyarrhythmias can lead to ventricular dysfunction and HF (Table 1). Atrial tachycardia (AT) is a classic arrhythmia that can result in AiCMP when it is incessant. In studies of focal AT in adults, T-CMP was reported between 8.3% and 10% of patients. Permanent form of junctional reciprocating tachycardia, although a rare condition, is usually incessant and is typically associated with AiCMP. However, other arrhythmias which are not typically associated with AiCMP, like atypical atrioventricular nodal reentrant tachycardia or fascicular ventricular tachycardia, can also be present in the occasional patient with reversible ventricular dysfunction when they are slow and incessant.

On the other hand, AF, the most common chronic arrhythmia in the general population, may be associated with varying degrees of ventricular dysfunction in many patients and may, therefore, be the most common cause of AiCMP. In patients with left ventricular (LV) dysfunction and AF, significant improvement in ejection fraction is seen in 58% to 68% after ablation suggesting that many of these patients have reversible ventricular dysfunction related to AF. In different studies of radiofrequency ablation (RFA) of PVCs, PVC-induced ventricular dysfunction varies between 7% and 30%.

Pathophysiology

AiCMP is a heterogenous condition and different pathophysiologic mechanisms underlie the development of ventricular dysfunction and HF secondary to the different triggers (Table 2).

A rapid heart rate is well known to result in ventricular dysfunction and HF but the exact mechanism behind this is not clear. Various animal models have consistently shown the development of ventricular dilatation and dysfunction in response to chronic rapid pacing. These hemodynamic changes typically plateau at 1 week, whereas cardiac output, ejection fraction, and cardiac volumes may continually deteriorate for up to 3 to 5 weeks.

Chronic rapid pacing induces changes at myocyte and myocardium level. Depletion of myocyte energy stores, mitochondrial dysfunction with increased activity of oxidative enzymes, myocyte elongation, decreased myocyte attachment with basement membrane, activation of proapoptotic cascades, and loss of myocytes are the major

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**Table 1. Tachyarrhythmias That Can Lead in Cardiomyopathy.**

| Tachyarrhythmias                     | Possible Mechanism                                      |
|--------------------------------------|--------------------------------------------------------|
| AF or atrial flutter with rapid     | Depletion of myocyte energy source                      |
| ventricular response                 | Myocardial ischemia                                     |
| Incessant or frequent paroxysmal     | Neurohormonal activation                                |
| AT                                   | PVC                                                    |
| Permanent junctional reciprocating   | Heart rate irregularity                                 |
| tachycardia                          | Inter and intraventricular dyssynchrony                 |
| Outflow tract or idiopathic left     | AV dyssynchrony                                         |
| ventricular tachycardia              | Post extrasystolic potentiation                          |
| AV nodal reentrant tachycardia or    | Sympathetic activation                                  |
| AV reentrant tachycardia (uncommon)  |                                                        |
| Dual AV node nonreentrant tachycardia|                                                        |

**Note:** AF, atrial fibrillation; AT, atrial tachycardia; AV, atrioventricular.

**Table 2. Pathophysiologic Mechanisms for AiCMP.**

| Triggers       | Possible Mechanism                                      |
|----------------|--------------------------------------------------------|
| Tachycardia    | Structural changes                                     |
|                | Electrical changes                                      |
|                | Depletion of myocyte energy source                      |
|                | Myocardial ischemia                                     |
|                | Neurohormonal activation                                |
| PVC            | Heart rate irregularity                                 |
|                | Inter and intraventricular dyssynchrony                 |
|                | AV dyssynchrony                                         |
|                | Post extrasystolic potentiation                          |
| Atrial         | Sympathetic activation                                  |
| fibrillation    |                                                        |

**Note:** AiCMP, arrhythmia-induced cardiomyopathy; AV, atrioventricular; PVC, premature ventricular complex.
changes seen. Significant loss of extracellular matrix is also seen.\textsuperscript{27} This weakens myocyte support and causes myocyte misalignment. This may contribute to biventricular dilatation with no change or thinning of ventricular wall.\textsuperscript{28}

Increase in contraction frequency is known to cause a progressive increase in myocardial contractility. But this force frequency relationship is blunted in AiCMP.\textsuperscript{29} T tubules depletion with loss of L-type calcium channels,\textsuperscript{30} decreased Ca transient,\textsuperscript{31–33} slow Ca uptake,\textsuperscript{34} and reduced Ca stores\textsuperscript{35} are seen to contribute to abnormal excitation contraction coupling.

Myocardial ischemia may lead to myocyte injury, ventricular dilatation, and dysfunction. Alteration in myocardial capillary structure and distribution with reduced subendocardial coronary flow reserve is seen in animal models of rapid heart rate-induced ventricular dysfunction.\textsuperscript{36,37} AF appears to cause AiCMP by mechanisms not limited to a rapid rate alone.\textsuperscript{8,18,22} Animal models have shown calcium mishandling due to heart rate irregularity in AF and this altered excitation contraction coupling may contribute to ventricular dysfunction.\textsuperscript{38} Heart rate irregularity is also seen to produce adverse hemodynamic effects\textsuperscript{39} and increased sympathetic activity.\textsuperscript{40} In addition to heart rate irregularity, loss of atrial kick in patients with AF may lead in ventricular underfilling, elevation of filling pressure, and sympathetic dysregulation.\textsuperscript{41} Further studies are needed to better understand the mechanisms behind AiCMP in AF.

Similarly, development of AiCMP in the presence of frequent PVCs is multifactorial. Major proposed mechanisms are heart rate irregularity, inter- and intraventricular dyssynchrony, AV dyssynchrony, postextrasystolic potentiation, and sympathetic activation.\textsuperscript{42} Animal models of PVC-induced cardiomyopathy failed to show inflammation, mitochondrial dysfunction, apoptosis, or fibrosis seen in other animal models of AiCMP.\textsuperscript{43} These findings are supported by CMR studies in patients with PVC-induced cardiomyopathy.\textsuperscript{44} Electrophysiological remodeling with altered Dyad function appears as a primary reason for PVC-induced cardiomyopathy.\textsuperscript{5} These findings suggest primary functional abnormalities behind this condition.

### Clinical Presentation

AiCMP may develop within months of onset of the arrhythmia or it may take years.\textsuperscript{45} In general, more rapid arrhythmia results in rapid onset of ventricular dysfunction while a slower arrhythmia may take longer to produce ventricular dysfunction. It resembles dilated cardiomyopathy in phenotype. Most common presentations are palpitation, HF, and presyncope or syncope.\textsuperscript{46} Patients may also be asymptomatic. Risk of sudden death appears increased in these patients and this may be the first presentation.\textsuperscript{10,47}

### Diagnosis and Management

#### When to Suspect?

In a patient with ventricular dysfunction with no clear cause and persistent or frequent paroxysmal arrhythmia, AiCMP is a potential diagnosis. In patients with paroxysmal arrhythmias or PVCs, ambulatory electrocardiographic (ECG) monitoring may be useful to identify the culprit arrhythmia.\textsuperscript{6} Ambulatory ECG monitoring for relatively long duration (2 weeks) may better identify the culprit arrhythmia and provide more accurate measure of PVC burden. In a study, 24-hour ambulatory ECG monitoring identified only 53% patients with PVC burden >10%. Yield of ambulatory ECG monitoring continuously increased with increasing duration of monitoring.\textsuperscript{48}

Although AiCMP is typically seen without other structural heart disease, some patients with structural heart disease develop ventricular dysfunction out of proportion to the underlying cardiac condition in presence of persistent or frequent paroxysmal arrhythmia. In all such patients, arrhythmia may be additionally responsible for the ventricular dysfunction.

On echocardiogram, AiCMP is characterized by biventricular dilatation with lack of ventricular hypertrophy. When compared with idiopathic dilated cardiomyopathy (DCM), patients with AiCMP are found to have smaller LV-end diastolic dimensions and less LV mass index for similar degree of ventricular dysfunction.\textsuperscript{49}

B-type natriuretic peptide (BNP) and N terminal pro B-type natriuretic peptide (NT pro BNP) levels are usually elevated in patients with ventricular dysfunction. In patients with ventricular dysfunction, fall of plasma BNP and/or NT pro BNP level after successful suppression of arrhythmia may help in differentiating AiCMP from idiopathic DCM.\textsuperscript{50}

### Predicting Improvement: Role of Cardiac Magnetic Resonance in AiCMP

Cardiac magnetic resonance (CMR) may assist in assessing ventricular dimensions and function and may also help in differentiating patients of AiCMP from idiopathic DCM patients. CMR may also predict response to treatment in patients with suspected AiCMP. In a study of idiopathic ventricular arrhythmias and ventricular dysfunction, late gadolinium enhancement (LGE) was more prevalent in patients who did not respond well after ablation.\textsuperscript{44} Another study in patients with frequent PVCs and ventricular dysfunction has shown LGE as independent predictor of response to ablation.\textsuperscript{51} In the recent CAMERA-MR study of AF with ventricular dysfunction, absence of LGE predicted significant improvement in ventricular function after AF.
ablation. A follow-up CMR after successful treatment of arrhythmia may be done to look for residual fibrosis or scar which may give important prognosis information.

**Treatment: Drugs Versus Ablation**

Initial treatment of AiCMP is optimization of HF therapy with standard drugs (beta blocker, ACE inhibitors/angiotensin receptor blockers, mineralocorticoid receptor antagonists, and Diuretics) to relieve symptoms of HF and attenuate ventricular remodeling. As suppression of arrhythmia can completely or partially reverse ventricular dysfunction in AiCMP, the main component of management is effective suppression of arrhythmia with antiarrhythmic drugs (AADs) or RFA.

Selection of strategy to suppress arrhythmia depends on type of arrhythmia, patient status, and associated comorbidities. For arrhythmias such as atrial flutter, atrioventricular nodal re-entrant tachycardia, atrioventricular reentrant tachycardia, and focal AT, RFA has high success rate and should be considered as first line of treatment.

In a patient with ventricular dysfunction and persistent or paroxysmal AF, first target is adequate rate control. If the patient continues to worsen even after appropriate rate control, establishing sinus rhythm should be the goal. AADs have shown lower success rate (35%-70%) in achieving sinus rhythm with frequent adverse effects in AF. Although studies of AF ablation have shown better success rate (70%-90%) and fewer adverse effects, repeat ablation was often required. Till now only 1 randomized controlled trial has directly compared AF ablation and amiodarone for rhythm control in patients with AF and HF. At the end of 2 years, ablation was found superior in establishing sinus rhythm as compared to amiodarone (70% vs 34%) with lower unplanned hospitalization and mortality.

Studies of rhythm control strategy with AADs have failed to show benefit over adequate rate control strategy. But recent randomized controlled trials of rhythm control strategy with AF ablation versus adequate rate control strategy have shown significant benefit in functional class and ejection fraction with AF ablation. Therefore, early rhythm control strategy with ablation may be considered as first-line treatment in suitable patients with AF.

More than 80% fall in PVC burden is considered as successful suppression of PVCs. Both AADs and RFA have shown long-term success rate of 70% to 80% in different studies. Beta blockers are the most frequently advised AAD for frequent PVCs because of the lack of significant side effects. Other AADs such as amiodarone, dofetilide, sotalol, mexiletine, or flecainide may be more effective than beta blockers but are associated with significant side effects and pro-arrhythmic risk. Current guidelines do not recommend use of Class IC drugs because of increased mortality observed with Class IC drugs in CAST trial.

**Long-Term Outcomes**

Initially, AiCMP was thought as a completely reversible entity but evidence suggests it may not be so. In tachycardia-induced ventricular dysfunction, ventricular function improves within a month after elimination of tachycardia, but may take up to 2 to 3 months. Even after normalization of ventricular systolic function, some dilatation of ventricle with diastolic dysfunction may persist. Patient may also show hypertrophic response after suppression of tachycardia. This denotes underlying histopathological abnormalities.

Studies have reported rapid development of ventricular dysfunction and HF after recurrence of arrhythmia. Persistent histopathological abnormalities may be responsible for this. Sudden deaths are also reported even after successful suppression of arrhythmia. Thus, a treatment option with high success or cure rate should be considered for management of AiCMP and one should monitor for recurrences.

**Conclusion and Future Perspectives**

Tachycardia, frequent PVCs, and AF can trigger ventricular dysfunction with or without an underlying cardiac condition. The term AiCMP encompasses all these conditions. AiCMP is a reversible cause of cardiomyopathy and mimics idiopathic DCM. Clinician has to keep a high index of suspicion to identify this condition. Ambulatory ECG monitoring may be required for diagnosis. Successful suppression of arrhythmia can improve or normalize ventricular function with decrease in morbidity and associated health care expenditure. The histopathological changes may persist and may contribute to rapid deterioration with recurrence of arrhythmia. Sudden cardiac death may occur. CMR may help in diagnosis and may predict response to therapy. A follow-up CMR may give important prognostic information.

Despite great progress in understanding and management of AiCMP, there are definitely gaps in the knowledge. We know little about pathophysiology of PVC-induced cardiomyopathy and AF-induced cardiomyopathy. There is less clarity on timing of interventions. We need more studies comparing ablation and AADs in PVC-induced cardiomyopathy. Our understanding regarding future events in these patients is limited. We need to define the role of CMR in these patients in management as well as in follow-up.
Declaration of Conflicting Interests
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

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References
1. Gossage AM, Braxton Hicks JA. On auricular fibrillation. Q J Med. 1913;6:435-440.
2. Whipple GH, Sheffield LT, Woodman EG, Theophilis C, Friedman S. Reversible congestive heart failure due to chronic rapid stimulation of the normal heart. Proc N Engl Cardiovasc Soc. 1962;20:39-40.
3. Duffee DF, W-K Shen, Smith HC. Suppression of frequent premature ventricular contractions and improvement of left ventricular function in patients with presumed idiopathic dilated cardiomyopathy. Mayo Clin Proc. 1998;73(5):430-433.
4. Chugh SS, W-K Shen, Luria DM, Smith HC. First evidence of premature ventricular complex-induced cardiomyopathy: a potentially reversible cause of heart failure. J Cardiovasc Electrophysiol. 2000;11(3):328-329.
5. Huizir JF, Ellenbogen KA, Tan AY, Kaszala K. Arrhythmia-induced cardiomyopathy. J Am Coll Cardiol. 2019;73(18):2328-2344.
6. Gopinathannair R, Etheridge SP, Marchlinski FE, Spinaile FG, Lakkiiredy D, Olshansky B. Arrhythmia-induced cardiomyopathy. J Am Coll Cardiol. 2015;66(15):1714-1728.
7. Martin CA, Lambiase PD. Pathophysiology, diagnosis and treatment of tachycardia-induced cardiomyopathy. Heart. 2017;103(19):1543-1552.
8. Marrouche NF, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med. 2018;378(5):417-427.
9. El Kadri M, Yokokawa M, Labounty T, et al. Effect of ablation of frequent premature ventricular complexes on left ventricular function in patients with nonischemic cardiomyopathy. Heart Rhythm. 2015;12(4):706-713.
10. Watanabe H, Okamura K, Chiuishi M, et al. Clinical characteristics, treatment, and outcome of tachycardia induced cardiomyopathy. Int Heart J. 2008;49(1):39-47.
11. Moore JP, Patel PA, Shannon KM, et al. Predictors of myocardial recovery in pediatric tachycardia-induced cardiomyopathy. Heart Rhythm. 2014;11(7):1163-1169.
12. Wang NC. Dual atrioventricular nodal nonreentrant tachycardia: a systematic review. Pacing Clin Electrophysiol. 1996;19(9):1391-1392.
13. Singh B, Kaul U, Talwar KK, Wasir HS. Reversibility of "tachycardia induced cardiomyopathy" following the cure of idiopathic left ventricular tachycardia using radiofrequency energy. Pacing Clin Electrophysiol. 1996;19(9):1391-1392.
14. Ju W, Yang B, Li M, et al. Tachycardia-induced cardiomyopathy complicated by focal atrial tachycardia: incidence, risk factors, and long-term outcome: AT-induced cardiomyopathy. J Cardiovasc Electrophysiol. 2014;25(9):953-957.
15. Medi C, Kalman JM, Haqqani H, et al. Tachycardia-mediated cardiomyopathy secondary to focal atrial tachycardia. J Am Coll Cardiol. 2009;53(19):1791-1797.
16. Kang KT, Etheridge SP, Kantoch MJ, et al. Current management of focal atrial tachycardia in children: a multicenter experience. Circ Arrhythm Electrophysiol. 2014;7(4):664-670.
17. Selvaraj R, Ananthakrishnanpillai A, Sadasivam R, Balachander J. “Pseudo PJRT”-fast-slow AV nodal reentrant tachycardia presenting with tachycardia-induced cardiomyopathy. Pacing Clin Electrophysiol. 2013;36(1):e4-e6.
18. Prabhu S, Taylor AJ, Costello BT, et al. Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction. J Am Coll Cardiol. 2017;70(16):1949-1961.
19. Bogun F, Crawford T, Reich S, et al. Radiofrequency ablation of frequent, idiopathic premature ventricular complexes: comparison with a control group without intervention. Heart Rhythm. 2007;4(7):863-867.
20. Baman TS, Lange DC, Ilg KJ, et al. Relationship between burden of premature ventricular complexes and left ventricular function. Heart Rhythm. 2010;7(7):865-869.
21. Hasdemir C, Ulucan C, Yavuzgil O, et al. Tachycardia-induced cardiomyopathy in patients with idiopathic ventricular arrhythmias: the incidence, clinical and electrophysiologic characteristics, and the predictors. J Cardiovasc Electrophysiol. 2011;22(6):663-668.
22. Shinbne JS, Wood MA, Jensen DN, Ellenbogen KA, Fitzpatrick AP, Scheinman MM. Tachycardia-induced cardiomyopathy: a review of animal models and clinical studies. J Am Coll Cardiol. 1997;29(4):709-715.
23. Coleman HN, Taylor RR, Pool PE, et al. Congestive heart failure following chronic tachycardia. Am Heart J. 1971;81(6):790-798.
24. O’Brien PJ, Ianuzzo CD, Moe GW, Stoppes TP, Armstrong, PW. Rapid ventricular pacing of dogs to heart failure: biochemical and physiological studies. Can J Physiol Pharmacol. 1990;68(1):34-39.
25. Zellner JL, Spinaile FG, Eble DM, Hewett KW, Crawford FA. Alterations in myocyte shape and basement membrane attachment with tachycardia-induced heart failure. Circ Res. 1991;69(3):590-600.
26. Kajstura J, Zhang X, Liu Y, et al. The cellular basis of pacing-induced dilated cardiomyopathy: myocyte cell loss and myocyte cellular reactive hypertrophy. Circulation. 1995;92(8):2306-2317.
27. Spinaile FG, Tomita M, Zellner JL, Cook JC, Crawford FA, Zile MR. Collagen remodeling and changes in LV function during development and recovery from supraventricular tachycardia. Am J Physiol-Heart Circ Physiol. 1991;261(2):H308-H318.
28. Tomita M, Spinaile FG, Crawford FA, Zile MR. 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):635-644.
29. Eising GP, Hammond HK, Helmer GA, Gilpin E, Ross J. Force-frequency relations during heart failure in pigs. Am J Physiol-Heart Circ Physiol. 1994;267(6):H2516-H2522.
30. Balijepalli R. Depletion of T-tubules and specific subcellular changes in sarcosomal proteins in tachycardia-induced heart failure. *Cardiovasc Res.* 2003;59(1):67-77.

31. Mukherjee R, Hewett K, Spinale F. Myocyte electrophysiologic properties following the development of supraventricular tachycardia-induced cardiomyopathy. *J Mol Cell Cardiol.* 1995;27(6):1333-1348.

32. Mukherjee R, Hewett KW, Walker JD, Basler CG, Spinale FG. Changes in L-type calcium channel abundance and function during the transition to pacing-induced congestive heart failure. *Cardiovasc Res.* 1998;37(2):432-444.

33. Vatner DE, Sato N, Kiuchi K, Shannon RP, Vatner SF. Decrease in myocardial ryanodine receptors and altered excitation-contraction coupling early in the development of heart failure. *Circulation.* 1994;90(3):1423-1430.

34. Perreault CL, Shannon RP, Komamura K, Vatner SF, Morgan JP. Abnormalities in intracellular calcium regulation and contractile function in myocardium from dogs with pacing-induced heart failure. *J Clin Invest.* 1992;89(3):932-938.

35. Cory CR, McCutcheon LJ, O’Grady M, Pang AW, Geiger JD, O’Brien PJ. Compensatory downregulation of myocardial Ca channel in SR from dogs with heart failure. *Am J Physiol-Heart Circ Physiol.* 1993;264(3):H926-H937.

36. Spinale FG, Grine RC, Tempel GE, Crawford FA, Zile MR. Alterations in the myocardial capillary vasculature accompanying tachycardia-induced cardiomyopathy. *Basic Res Cardiol.* 1992;87(1):65-79.

37. Shannon RP, Komamura K, Shen YT, Bishop SP, Vatner SF. Impaired regional subendocardial coronary flow reserve in conscious dogs with pacing-induced heart failure. *Am J Physiol-Heart Circ Physiol.* 1993;265(3):H801-H809.

38. Ling L, Khammy O, Byrne M, et al. Irregular rhythm adversely influences calcium handling in ventricular myocardium: implications for the interaction between heart failure and atrial fibrillation. *Circ Heart Fail.* 2012;5(6):786-793.

39. Clark DM, Plumb VJ, Epstein AE, Kay GN. Hemodynamic effects of an irregular sequence of ventricular cycle lengths during atrial fibrillation. *J Am Coll Cardiol.* 1997;30(4):1039-1045.

40. Wasmund SL, J-M Li, Page RL, et al. Effect of atrial fibrillation and an irregular ventricular response on sympathetic nerve activity in human subjects. *Circulation.* 2003;107(15):2011-2015.

41. Trulock KM, Narayan SM, Piccini JP. Rhythm control in heart failure patients with atrial fibrillation. *J Am Coll Cardiol.* 2014;64(7):710-721.

42. Y-M Cha, Lee GK, Klarich KW, Grogan M. Premature ventricular contraction-induced cardiomyopathy: a treatable condition. *Circ Arrhythm Electrophysiol.* 2012;5(1):229-236.

43. Huizar JF, Kaszala K, Potfay J, et al. Left ventricular systolic dysfunction induced by ventricular ectopy: a novel model for premature ventricular contraction-induced cardiomyopathy. *Circ Arrhythm Electrophysiol.* 2011;4(4):543-549.

44. Hasdemir C, Yuksel A, Camli D, et al. Late gadolinium enhancement CMR in patients with tachycardia-induced cardiomyopathy caused by idiopathic ventricular arrhythmias. *Pacing Clin Electrophysiol.* 2012;35(4):465-470.

45. Bozkurt B, Colvin M, Cook J, et al. Current diagnostic and treatment strategies for specific dilated cardiomyopathies: a scientific statement from the American Heart Association. *Circulation.* 2016;134(23):e579-e646.

46. Donghua Z, Jian P, Zhongbo X, et al. Reversal of cardiomyopathy in patients with congestive heart failure secondary to tachycardia. *J Interv Card Electrophysiol.* 2013;36(1):27-32.

47. Nerheim P, Birger-Botkin S, Piracha LA, Olshansky B. Heart failure and sudden death in patients with tachycardia-induced cardiomyopathy and recurrent tachycardia. *Circulation.* 2004;110(3):247-252.

48. Loring Z, Hanna P, Pellegrini CN. Longer ambulatory ECG monitoring increases identification of clinically significant ectopy. *Pacing Clin Electrophysiol.* 2016;39(6):592-597.

49. Y-H Jeong, K-J Choi, J-M Song, et al. Diagnostic approach and treatment strategy in tachycardia-induced cardiomyopathy. *Clin Cardiol.* 2008;31(4):172-178.

50. Nia AM, Gassanov N, Dahlem KM, et al. Diagnostic accuracy of NT-proBNP ratio (BNP-R) for early diagnosis of tachycardia-mediated cardiomyopathy: a pilot study. *Clin Res Cardiol.* 2011;100(10):887-896.

51. Penela D, Van Huls Vans Taxis C, Aguina CA, L., et al. Neurohormonal, structural, and functional recovery pattern after premature ventricular complex ablation is independent of structural heart disease status in patients with depressed left ventricular ejection fraction. *J Am Coll Cardiol.* 2013;62(13):1195-1202.

52. Ling L, Kalman JM, Ellims AH, et al. Diffuse ventricular fibrosis is a late outcome of tachycardia-mediated cardiomyopathy after successful ablation. *Circ Arrhythm Electrophysiol.* 2013;6(4):697-704.

53. Roy D, Talajic M, Dorian P, et al. Amiodarone to prevent recurrence of atrial fibrillation. *N Engl J Med.* 2000;342(13):913-920.

54. Shetron RJ, Clark AL, Goode K, et al. A randomised, controlled study of rate versus rhythm control in patients with chronic atrial fibrillation and heart failure: (CAFE-II Study). *Heart.* 2009;95(11):924-930.

55. Chen MS, Marrouche NF, Khaykin Y, et al. Pulmonary vein isolation for the treatment of atrial fibrillation in patients with impaired systolic function. *J Am Coll Cardiol.* 2004;43(6):1004-1009.

56. Gentlesk PJ, Sauer WH, Gerstenfeld EP, et al. Reversal of left ventricular dysfunction following ablation of atrial fibrillation. *J Cardiovasc Electrophysiol.* 2007;18(1):9-14.

57. Di Biase L, Mohanty P, Mohanty S, et al. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. *Circulation.* 2016;133(17):1637-1644.

58. Al-Khatib SM, Shaw LK, Lee KL, O’Connor C, Califf RM. Is rhythm control superior to rate control in patients with atrial fibrillation and congestive heart failure. *Am J Cardiol.* 2004;94(6):797-800.

59. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med.* 2008;358(25):2667-2677.

60. Anastasiou-Nana MI, Menlove RL, Nanas JN, Anderson JL. Changes in spontaneous variability of ventricular ectopic activity as a function of time in patients with chronic atrial arrhythmias. *Circulation.* 1988;78(2):286-295.
61. Pratt CM, Moyé LA. The cardiac arrhythmia suppression trial: casting suppression in a different light. *Circulation*. 1995; 91(1):245-247.

62. Hyman MC, Mustin D, Supple G, et al. Class IC antiarrhythmic drugs for suspected premature ventricular contraction-induced cardiomyopathy. *Heart Rhythm*. 2018; 15(2):159-163.

63. Zhong L, Y-H Lee, X-M Huang, et al. Relative efficacy of catheter ablation vs antiarrhythmic drugs in treating premature ventricular contractions: a single-center retrospective study. *Heart Rhythm*. 2014;11(2):187-193.

64. Yokokawa M, Good E, Crawford T, et al. Recovery from left ventricular dysfunction after ablation of frequent premature ventricular complexes. *Heart Rhythm*. 2013; 10(2):172-175.

65. Dandamudi G, Rampurwala AY, Mahenthiran J, Miller JM, Das MK. Persistent left ventricular dilatation in tachycardia-induced cardiomyopathy patients after appropriate treatment and normalization of ejection fraction. *Heart Rhythm*. 2008;5(8):1111-1114.