Received: 25 May 2018 | Accepted: 14 June 2018

DOI: 10.1002/joa3.12094

SPECIAL ISSUE: RISK STRATIFICATION AND SPECIFIC MANAGEMENT

WILEY Journal of Arrhythmia Open Access

# Arrhythmia induced cardiomyopathy

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## Abstract

Arrhythmia induced cardiomyopathies (AIC) refer to the collective condition of Arrhythmia, Tachycardia, and ectopy-induced Cardiomyopathy. Atrial fibrillation (AF) and heart failure (HF) are modern epidemics that often coexist and exacerbate one another. We aim to provide an overview of the current understanding and evidence for treatment and management in AIC with a particular focus on AF-mediated cardiomyopathy and suggest approaches to recognize, screen, and manage AIC.

**KEYWORDS**

arrhythmia, atrial fibrillation, cardiomyopathy, reversible, tachycardia

## 1 | INTRODUCTION

Arrhythmias represent an important reversible cause for left ventricular systolic dysfunction.[1–8] However, arrhythmias may be under recognized leading to a delay in intervention.[9] With the advent of catheter ablation, an effective tool is available which can restore sinus rhythm without the detrimental effects of drug toxicity.[9,10] For the purpose of this review, we will use the term *Arrhythmia-induced cardiomyopathies* (AIC) to refer to the collective condition of Tachycardia and ectopy-induced Cardiomyopathy.

Atrial fibrillation (AF) and heart failure (HF) are modern epidemics that often coexist and exacerbate one another.[11] CAMERA-MRI [7]and CASTLE-AF[2] are two pivotal studies which highlight the role of atrial fibrillation in systolic heart failure. We aim to provide an overview of the current understanding and evidence for treatment and management in AIC with a particular focus on AF-mediated cardiomyopathy and suggest approaches to recognize, screen, and manage AIC.

## 2 | WHAT IS AIC?

Arrhythmia induced cardiomyopathies was first described in 1913 but it was not until 1962 that the reversible nature of the condition was appreciated.[12,13] AIC is defined by sufficient supraventricular or ventricular arrhythmia to result in Left ventricular (LV) systolic dysfunction.[9] The arrhythmia can either be sustained, paroxysmal, or highly frequent ectopic activity.[9,14,15] The arrhythmia duration which preceded the development of LV dysfunction is often difficult to determine as symptom onset is often insidious with progressive fatigue and dyspnea without palpitations. In animal models, AIC can be reproduced with rapid pacing for 1-2 months.[16] Once the arrhythmia is corrected recovery of LV function is seen within 6 weeks.[10] Most patients with AIC can expect to improve their LV function to normal levels with an overall favorable prognosis. Nonetheless there is a small risk of sudden cardiac death particularly in the setting of arrhythmia recurrence or where the cardiomyopathy is of mixed etiology including coronary disease.[10,17] AIC can occur with a wide range of arrhythmia (Table 1). The prevalence of AIC is estimated at 8%-28% with focal atrial tachycardia (FAT) and 10%-34% of patients with premature ventricular complex (PVC) and nonsustained ventricular tachycardia (VT).[18] Only until recently has the definition of AIC started to include arrhythmias other than tachycardia.[8]

Arrhythmia induced cardiomyopathies has a wide range of clinical presentations and may be entirely responsible for the cardiomyopathy (Type 1) or be contributory to an underlying CM with an alternate etiology (Type 2).[19] Hence, two categories of AIC have been proposed.[9,20]

- Type 1 AIC: Arrhythmia induced. This is when arrhythmia is solely responsible for AIC and the LV function returns to normal upon successful treatment of the arrhythmia.[9]

**TABLE 1** A wide range of atrial and ventricular arrhythmias have been reported in association with AIC has been listed

| Causes of tachycardia-mediated AIC | |
|---|---|
| Supraventricular | Atrial fibrillation[2,7] |
| | Ectopic atrial tachycardia[25,26] |
| | Atrial flutter |
| | Atrioventricular nodal re-entry tachycardia |
| | Atrioventricular tachycardia |
| | Permanent junctional reciprocating tachycardia |
| Ventricular | Premature ventricular contraction (PVC)[14,54] |
| | Ventricular tachycardia (high burden) |

- Type 2 AIC: Arrhythmia mediated. Arrhythmia exacerbates the underlying cardiomyopathy and treatment of the arrhythmia results in partial resolution of the cardiomyopathy.[9]

## 3 | PATHOPHYSIOLOGY OF AIC

Arrhythmia induced cardiomyopathies appears to be mediated through the following three mechanisms with considerable overlap between these factors (Figure 1):

1. Tachycardia
2. Irregular rhythm
3. Dyssynchrony

In animal models, LV dysfunction is relatively reproducible with rapid pacing resulting in LV dysfunction within weeks of tachycardia onset. Three phases have been reported in this phenotype.[9]

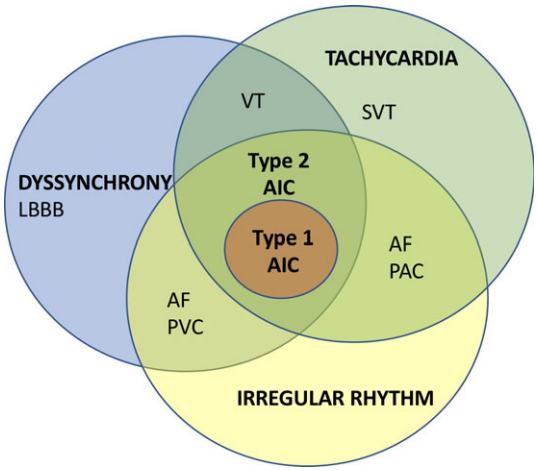


**FIGURE 1** Mechanistic Overlap in AIC. Schematic representation of the mechanisms implicated in AIC with considerable overlap between these factors. AIC: Arrhythmia-mediated cardiomyopathy, SVT: Supraventricular tachycardia, AF: Atrial fibrillation, PAC: Premature atrial complex, PVC: Premature ventricular complex, VT: Ventricular tachycardia, LBBB: Left bundle branch block

Phase 1: Compensatory phase (>7 days). During this phase, there is increased neurohormonal activation with early changes to the extra cellular matrix and preserved LV systolic function.
Phase 2: LV dysfunction phase (1-3 weeks). Continued neurohormonal activation and upregulation of the renin angiotensin system. There is cellular remodeling, contractile dysfunction with LV systolic dysfunction and dilatation.
Phase 3: LV failure phase (>3 weeks). Further adverse LV remodeling with pump failure, severe dilatation, and abnormal intracellular calcium handling.

In humans, AIC is more unpredictable with a second factor, likely a genetic susceptibility, to explain why a similar burden of arrhythmia can have such variable effects on systolic function in different individuals.[10] Tachycardia at >100 bpm[4] and >15% of the day has the potential to result in AIC.[20] Timing of onset of arrhythmia to clinical presentation or LV deterioration can vary widely and depend on duration of sustained arrhythmia, coexisting structural heart disease, and patients' age. The mechanism of tachycardia-mediated cardiomyopathy is not fully understood, however, may include subclinical ischemia, redox stress, abnormal calcium handling, and resultant disruption to energy storage with ATP depletion. At a cellular level there is myofibril misalignment, cellular elongation, sarcomere loss, and myocyte depletion[4,16,21] resulting in an increase in LV end diastolic diameter (LVEDD). Neurohormonal activation is characterized by elevated levels of Epinephrine, norepinephrine, renin-aldosterone activity, and plasma atrial natriuretic peptide.[22] (See Figure 2).

## 4 | TACHYCARDIA AND AIC

Focal atrial tachycardia is a well-recognized cause of AIC with an incidence of AIC in patients with FAT of 8.3%-10%.[23,24] Medi et al reported the largest series to date of 30 patients (with incessant AT in 29) with focal atrial tachycardia and LV systolic dysfunction from a total population of 345 patients undergoing catheter ablation for FAT over a 10 year period.[25] Tachycardia cycle length and ventricular response rates were slower in patients with TCM than in patients with FAT and preserved LV systolic function. The pulmonary veins and crista terminalis (Figure 3) were more common anatomic sites for incessant tachycardia.[26] Catheter ablation was successful in 25 of 30 patients with TCM with complete recovery of LV function in 96%.

Atrial Flutter may be associated with LV dysfunction in up to 25% with majority of cases improving their LV function after termination of arrhythmia.[27]

Supraventricular tachycardia (SVT) such as Atrioventricular nodal reciprocating tachycardia (AVNRT),[28] and Atrioventricular reciprocating tachycardia (AVRT) are rarely associated with AIC as episodes are not sufficiently frequent.[29] However, junctional reciprocating tachycardia (PJRT), is a more persistent form of SVT that is more common in children and has an increased association with AIC.[15]

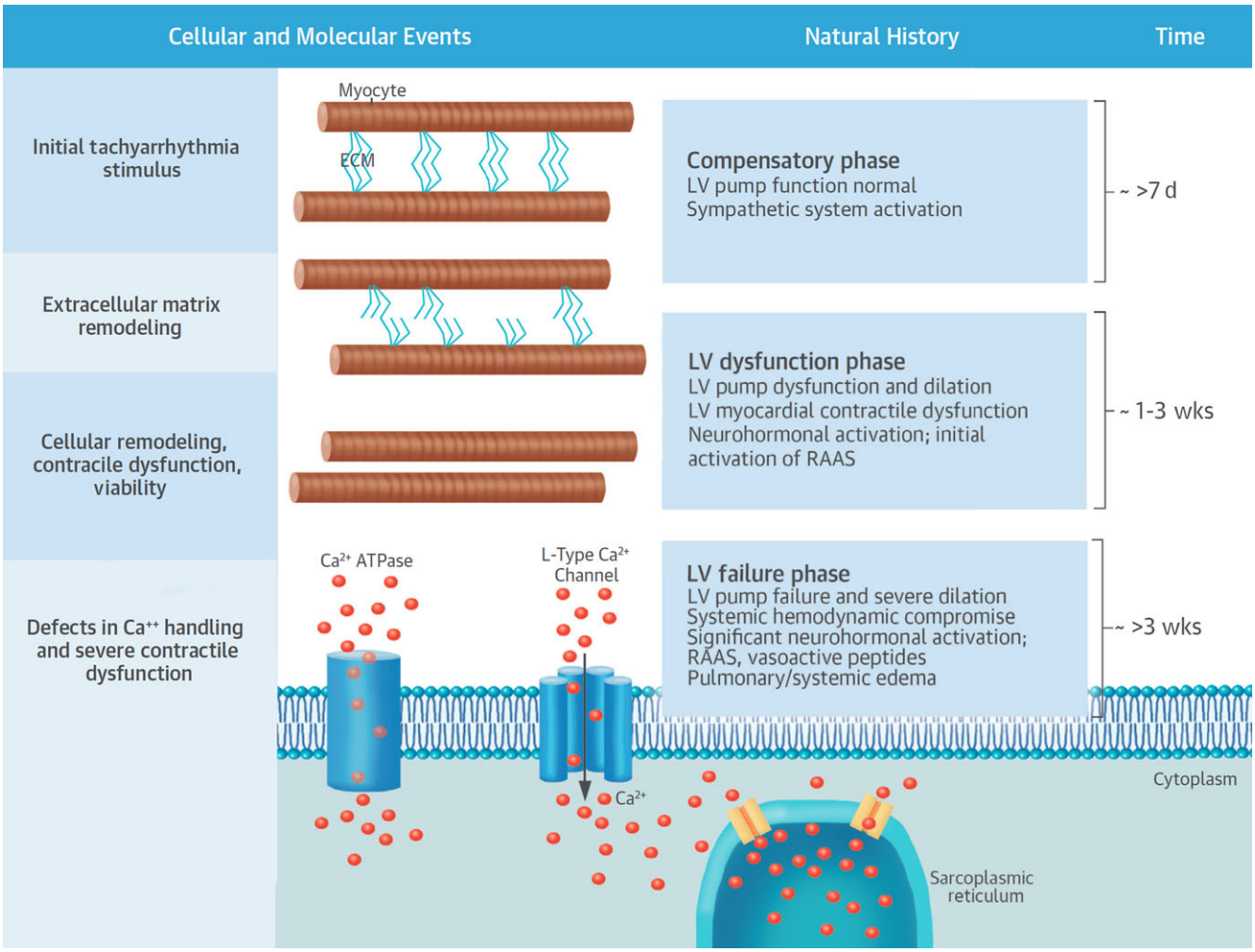


**FIGURE 2** Cellular and Molecular Changes in Myocardium with Tachycardia. Time-dependant and predictable cellular and molecular response to rapid ventricular pacing in animals that involve both extracellular matrix (ECM) and myocyte remodeling. There is loss of extracellular matrix and architecture that occurs over three phases: Compensatory (>7 days), LV dysfunction phase (1-3 wk), LV failure (>3 wk). LV: Left ventricle. ATPase: adenosine triphosphatase; RAAS: renin-angiotensin-aldosterone system. (Credit: Reprinted from, JACC, Vol 66/Issue 15, Gopinathannair R et al, Arrhythmia-Induced Cardiomyopathies Mechanisms, Recognition, and Management, Pages No1714-1728., Copyright (2015), with permission from Elsevier)

Idiopathic Ventricular tachycardia (VT) arising from the outflow tract, if frequent or persistent, can lead to AIC. Responsible foci often originate from, but are not limited to, the right ventricular outflow tract (RVOT) and carries a good prognosis once arrhythmia is ablated and LV function restored.[30] In one series, 7% of patients with frequent PVC's had sustained monomorphic VT and 7% of them had AIC.[31]

## 5 | AF-MEDIATED CARDIOMYOPATHY

Atrial fibrillation is the most common cause of AIC in adults[9,10,32] and the association between AF and AIC has been well described. AF and HF are modern epidemics which often coexist and precipitate one another.[11] In the Framingham study, those with AF had a higher risk of developing HF (HR of 2.22 [CI 1.47-3.34] $P < 0.0001$).[11] The pathophysiologic mechanisms underlying development or progression of cardiomyopathy in patients with AF include: tachycardia, heart rate irregularity, loss of atrial systolic function, and genetic factors.

Irregular contraction leads to adverse hemodynamic consequences that are independent of heart rate.[33,34] The contribution of irregularity is demonstrated in patients with rate controlled AF and LV dysfunction, who improve LV function following atrioventricular nodal ablation which regularizes ventricular rhythm with pacing.[33,35]Furthermore, atrioventricular dyssynchrony can impair diastolic filling which in turn worsens diastolic function thereby leading to increased left sided pressure and negative atrial remodeling which in turn perpetuates AF.[36,37] Coordinated atrial contraction contributes up to 20% of cardiac output and loss of atrial contraction adversely affects cardiac output in AF.[8,33,38]

It is likely that AF unmasks an underlying tendency and susceptibility to develop cardiomyopathy in patients with AIC.[37] A wide range of genetic mutations such as encoding molecules involved in

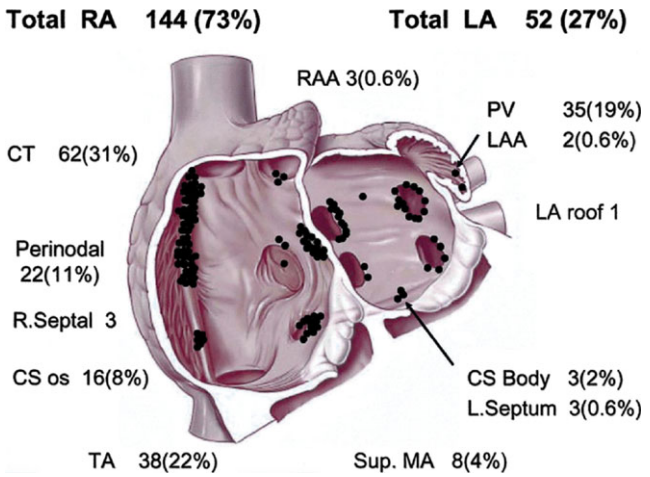


**FIGURE 3** Ectopic Atrial Tachycardia Sources. A schematic representation of the anatomic distribution of focal atrial tachycardias. CS: coronary sinus; CT: crista terminalis; LA: left atrium; LAA: left atrial appendage; MA: mitral annulus; PV: pulmonary vein; RA: right atrium; RAA: right atrial appendage; TA: tricuspid annulus. (Credit: Reprinted from, JACC, Vol 48 / Issue 5, Kistler, P et al, P-Wave Morphology in Focal Atrial Tachycardia Development of an Algorithm to Predict the Anatomic Site of Origin, Pages No1010-1017., Copyright (2006), with permission from Elsevier)

contractile function, cellular integrity and/or cytoskeletal structure have been implicated in nonischemic cardiomyopathy.[39] More than 50 causative genes have been implicated in dilated cardiomyopathy (DCM) and may be identified in up to 30% of patients. The four major genes include titin (*TTN*), lamin A/C (*LMNA*), β-myosin heavy chain (*MYH7*), and cardiac troponin T (*TNNT2*) genes.[40]

Until recently rate control was thought to be adequate in the management of AF-induced AIC.[9,41] The AF-CHF trial did not show a survival advantage in patients with NYHA class 2/3 heart failure symptoms and LVEF < 35% randomized to pharmacologic rate control vs rhythm control. However, multiple randomized studies (See Table 2) with catheter ablation as the rhythm control strategy have demonstrated the superiority of restoring sinus rhythm with ablation when compared with pharmacologic therapy.[42–46] A systematic review of 19 studies (914 patients) showed a 13.3% (95% CI 115 to 16%) improvement in LV EF in patients who underwent catheter ablation to restore sinus rhythm.[47] Although current heart failure guidelines are yet to include AF ablation in people with HF this is likely to change particularly in light of the recent CAMERA-MRI and CASTLE-AF trials.[1,6,7]

In the CAMERA-MRI trial,[7] 68 patients with persistent AF and idiopathic cardiomyopathy (EF < 45%) were randomized (1:1) to optimal rate control or catheter ablation to restore sinus rhythm and followed up for 6 months. Patients with significant coronary artery disease and other structural causes for cardiomyopathy were excluded. The average age was 60 years with an EF of 33 ± 8.6% and a $CHA_2DS_2Vasc$ score of 2.4 ± 0.9. All patients were well established on antifailure medications with 97% on beta blockade and 94% on renin angiotensin aldosterone system inhibition. A 4-week run in period ensured optimization of rate control in both groups with a resting heart rate of 78 ± 18 bpm. Patients randomized to catheter ablation underwent pulmonary vein isolation and posterior wall isolation[48] with arrhythmic burden documented with an implantable loop recorder. The primary endpoint was highly significant with an absolute EF improvement of 18.3% in the catheter ablation arm compared to 4.4% in the medical rate control arm ($P < 0.0001$). Absence of late gadolinium enhancement (LGE) on MRI portended better outcomes with an absolute improvement in LVEF of 22% in LGE negative compared with 11% in LGE positive group ($P = 0.0069$). Fifty-eight percent of patients in the catheter ablation arm normalized their EF compared with only 9% in the rate control arm. Catheter ablation was associated with improvements in NYHA class and reduction in BNP.

The landmark CASTLE-AF[2] study was a multi-center international study that randomized 363 patients to ablation vs medical therapy (rate or rhythm control). There were important differences in the study population compared to the CAMERA MRI trial. Inclusion criteria were both paroxysmal and persistent AF, LVEF ≤ 35% of ischemic (40%-50%) and/or nonischemic origin. All patients had a dual chamber implantable cardioverter-defibrillator (ICD) or cardiac resynchronization defibrillator (CRT-D).

The primary end point of a composite of death from any cause or heart failure hospitalization was significantly lower in the ablation arm (51 patients [28.5%] vs 82 patients [44.6%]; HR 0.62; 95% CI 0.43-0.87; $P = 0.007$) at a median follow up of 37 months. Major secondary end points of death from any cause were significantly fewer in the ablation arm (24 [13.4%] vs 46 [25%]; HR, 0.53; $P = 0.01$) with fewer hospitalization for worsening heart failure (37 [20.7] vs 66 [35.9]; HR 0.56; $P = 0.004$) or cardiovascular death (HR 0.49; $P = 0.009$). Ejection fraction improved by an absolute 8% at 60 months in the ablation group compared with 0% in the medical group. Subgroup analysis demonstrated greater benefit in LVEF of 25%-35% vs <25%. Both lower mortality and heart failure admission contributed to the primary endpoint, but heart failure effects were apparent much earlier at 6 months compared to a mortality benefit which became significant at 3 years. The cornerstone of the ablation strategy was pulmonary vein isolation (PVI) with additional ablation at the discretion of the operator. The AF burden in the ablation group was 20%-27% compared with 48%-64% in the medical group.

These 2 significant trials demonstrate the importance of restoration of sinus rhythm with catheter ablation in patients with AF and systolic heart failure with improvements in LVEF, quality of life, heart failure hospitalization and total mortality.

## 6 | PVC CARDIOMYOPATHY

The incidence of AIC in patients with PVC's has been estimated between 9% and 34%.[18,31] The mechanism responsible for PVC-induced cardiomyopathy is likely explained by[8] ventricular dyssynchrony and abnormal ventricular contraction.[49] The mechanism is akin to that seen in RV pacing-induced cardiomyopathy with redistribution of myocardial strain and work,[50] decreased adrenergic

**TABLE 2** Randomized Trials of AF ablation in patients with systolic dysfunction has been summarized

| Trial name | Design | Number of patients | Type of AIC (ischemic vs nonischemic) | AF type | Baseline EF (in CM group) | LVEF after ablation | Strategy | Strategy in medical arm |
|---|---|---|---|---|---|---|---|---|
| Khan et al. 2008 NEJM (PABA-CHF) | Prospective, multi-center, randomized (PVI vs AV node and pacing) | 81 patients (41 ablation) | NonIsch CM 29.5% | PsAF 48.5% | Inclusion: EF ≤ 40%, Average EF 28% | +8.0 ± 8% vs AVndoe −1 ± 4.0% ($P < 0.001$) | AV node ablation with BiV pacing vs PVI | NA |
| McDonald et al. 2011 Heart | Prospective, multi-center, randomized | 41 patients with CM (22 had RFA, 19 medical therapy) | DCM 22%, Isch CM 49% | PsAF 100% | Inclusion: EF < 35% | +8.2 ± 12% vs medical +1.4 ± 5.9% $P = 0.032$) | Medical therapy vs ablation | Rate control only |
| Jones et al. 2013 JACC | Prospective, multi-center, randomized | 52 patients (26 rate control & 26 ablation) | NonIsch CM 67% | PsAF 100% | Inclusion: EF < 35%, Mean 24% | +10.9 ± 11.5% $P < 0.001$ vs medical +5.4 ± 8.5% $P < 0.003$ | Medical therapy vs ablation | Rate control only |
| Hunter et al. 2014 Circ A E (CAMTAF) | Prospective single-center randomized | 50 patients with CM (24 rate control, 26 ablation) | DCM 31%, Isch CM 23% | PsAF 100% | Inclusion: EF < 50%, Average EF 33% | +8.1 ± 5.1% vs medical -3% ± 13% $P < 0.001$ | Medical therapy vs ablation | Rate control only |
| Prabhu et al. 2017 JACC (CAMERA-MRI) | Prospective multi-center randomized | 68 patients with CM | 100% DCM | PsAF 100% | Inclusion: EF ≤ 45%. Average EF 33 ± 8.6% | +18% ± 13% vs medical: 4.4% ± 13% $P < 0.0001$ | Medical therapy vs ablation | Rate control only |
| Marrouche et al. 2018 NEJM (CASTLE-AF) | Prospective multi-center randomized | 363 patients (184 medical vs 179 ablation) | DCM (NICM) 52%, Isch CM 46% | PsAF 67.5% | Inclusion: EF ≤ 35% Average EF 32% | +8% vs medical: 0.2% $P = 0.005$ | Medical therapy vs ablation | Rate or Rhythm control |

CM, Cardiomyopathy, DCM, Dilated cardiomyopathy, Isch CM, Ischemic cardiomyopathy, PsAF, Persistent AF, EF, Ejection fraction, AIC, Arrhythmia induced cardiomyopathy.

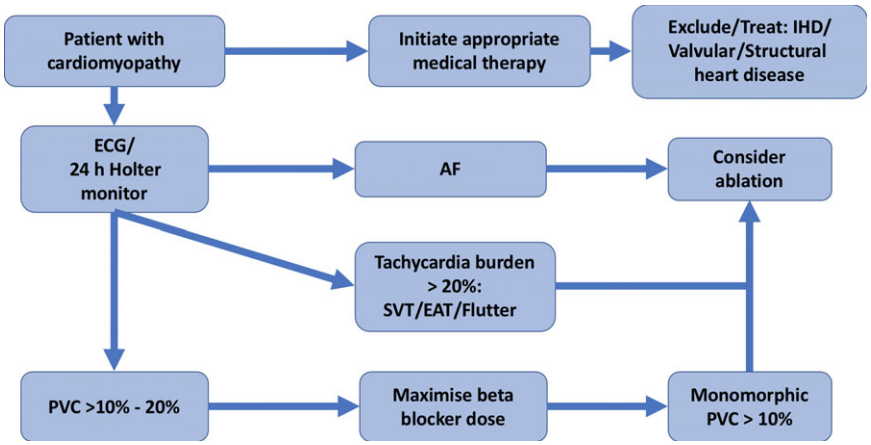


**FIGURE 4** Management Algorithm for Suspected AIC. A flow diagram for the management of suspected arrhythmia induced cardiomyopathy is presented here. ECG: Electrocardiography, PVC: Premature ventricular contractions, AF: Atrial fibrillation, SVT: Supraventricular tachycardia, IHD: Ischemic heart disease, EAT: Ectopic atrial tachycardia

innervation[34] and myocardial perfusion defects.[51] Five to 7 % of patients with outflow tract PVC's and tachycardia may develop AIC[14,31,52] and the threshold of PVC resulting in AIC ranged from 17 000 to 30 000 PVC / day (16%-24% total burden).[14,31,53,54] Importantly, AIC was not seen with a PVC burden of less than 10% and was predominantly confined to those with a PVC burden of >20%.[54] Penela et al suggested a PVC burden of ≥13% as the ideal cut off to predict LV recovery with a sensitivity of 100% and a specificity of 85% independent of coexistent structural heart disease.[55] In a retrospective study, catheter ablation was superior to antiarrhythmic therapy with beta blockers, calcium channel blockers, or amiodarone with a 93% reduction in PVCs[56] The benefit of PVC ablation was observed even in those with underlying structural heart disease with a EF improvement of 10%-15%.[57] Factors that may increase risk of AIC include: wider the QRS (>150 ms),[14,58] presence of nonsustained VT, multifocal PVC and RV PVC's.[59] Hence, any patient with LV dysfunction and a PVC burden of >20% should be considered for ablation or pharmacologic strategies to reduce arrhythmia burden.[60]

## 7 | MANAGEMENT OF AIC

Management algorithm for suspected AIC is presented in Figure 4. Although there are no specific recommendations in the guidelines defining the role of catheter ablation in patients with AF and HF, the evidence in favor of catheter ablation is mounting.[2,7,47] Catheter ablation is an effective tool in AIC and avoids the toxicity of rhythm control pharmacologic agents; however, it may not be effective or appropriate in all patients. Considerations should include the likely impact of rhythm correction on LV function. Namely patients with long-standing cardiomyopathy who develop an arrhythmia in the context of progression of the underlying disease are less likely to benefit than those presenting with the co diagnosis of LV systolic dysfunction and arrhythmia. Cardiac MRI may provide additional information as seen in the CAMERA-MRI trial[7,61] with the absence of LGE scar associated with greater recovery of LVEF. Patient comorbidities, patient preference, and the likelihood of successful and safe ablation are also important considerations.

## 8 | CONCLUSION

Arrhythmias are an under recognized cause of LV systolic dysfunction. Atrial fibrillation is the commonest form of arrhythmia responsible for cardiomyopathy with rate control alone inferior to restoration of sinus rhythm with catheter ablation. Catheter ablation in patients with AF and systolic dysfunction results in improvements in heart failure symptoms, LVEF with reductions in hospitalizations and total mortality, and should be considered first line in this patient population.

### CONFLICT OF INTEREST

Dr Sugumar is supported by co-funded NHMRC/NHF postgraduate scholarships & RACP JJ Billings scholarships. Dr Prabhu is supported by Baker institute, the European Heart Rhythm Association the Australian Government Department of Education and Training, Boston Scientific and Abbott. Dr Voskoboinik is supported by co-funded NHMRC/NHF postgraduate scholarships & Baker IDI Bright Sparks scholarships. Prof. Peter Kistler: None.

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**How to cite this article:** Sugumar H, Prabhu S, Voskoboinik A, Kistler PM. Arrhythmia induced cardiomyopathy. *J Arrhythmia*. 2018;34:376–383. https://doi.org/10.1002/joa3.12094