MECHANISMS AND CLINICAL SIGNIFICANCE
OF ARRHYTHMIA-INDUCED CARDIOMYOPATHY

Alexandre Raymond-Paquin MD¹,², Stanley Nattel MD¹,²,³,⁴, Reza Wakili MD⁵, Rafik Tadros MD PhD¹,²,⁶

¹Research Center, Montreal Heart Institute, Montreal, Quebec, Canada
²Faculty of Medicine, Université de Montréal, Montreal, Quebec, Canada
³Institute of Pharmacology, West German Heart and Vascular Center, Faculty of Medicine, University Duisburg-Essen, Essen, Germany
⁴Department of Pharmacology and Therapeutics, McGill University, Montreal, Canada
⁵Department of Cardiology and Vascular Medicine, West German Heart and Vascular Center Essen, University Duisburg-Essen, Essen, Germany
⁶Cardiovascular Genetics Center, Montreal Heart Institute, Montreal, Quebec, Canada

Short Title: Arrhythmia-Induced Cardiomyopathy
Word count: 8,362 (not counting title page)

Correspondence:
Rafik Tadros or Stanley Nattel
Montreal Heart Institute
5000 Bélanger
Montreal (QC)
H1T 3C8
rafik.tadros@umontreal.ca
stanley.nattel@icm-mhi.org
514-376-3330
Brief Summary

Arrhythmia-induced cardiomyopathy (AIC) is characterized by heart failure with left ventricular dysfunction for which the primary cause is the arrhythmia itself. The hallmark of this entity is its reversibility upon adequate arrhythmia control. This contemporary review will summarize the current understanding of pathophysiological mechanisms, discuss the clinical implications and offer a general approach to the management of AIC, with a particular focus on AIC in the context of atrial fibrillation.
ABSTRACT

Arrhythmia-induced cardiomyopathy (AIC) is characterized by left ventricular systolic dysfunction for which the primary cause is arrhythmia. The hallmark of AIC is its reversibility once the arrhythmia is properly controlled. Any tachyarrhythmia can potentially cause AIC (often called "tachycardiomyopathy"), with atrial fibrillation (AF) being by far the most common in clinical practice. The pathophysiological mechanisms underlying AIC need further clarification, but the available evidence, principally from animal models, implicates metabolic dysfunction due to increased oxygen requirements, neurohormonal adaptive mechanisms and cellular Ca\(^{2+}\) mishandling as important contributors. Tachycardia is a common denominator of most AIC-cases, but other components specific to the patient and the arrhythmia have been implicated. The diagnosis of AIC requires the exclusion of a primary causative role of other conditions such as hypertension, primary cardiomyopathies and valve disease, which may require specific pharmacological and invasive therapies. Catheter ablation is emerging as a safe and effective alternative to antiarrhythmic medication and has an established role in AIC management. Recent studies showing improved cardiac function and mortality-rate in patients with heart failure and concomitant AF dramatically illustrate the often-unrecognized scope of AIC and the potential benefits of interventional therapy. Major AF trials do not otherwise focus specifically on AIC, and careful analysis of the literature is necessary to appreciate the clinical characteristics and therapeutic implications. This contemporary review will summarize the current understanding of pathophysiological mechanisms underlying AIC, discuss the clinical implications and offer a general approach to the management, with a particular focus on AF-induced cardiomyopathy.
INTRODUCTION

Cardiac arrhythmias and heart failure (HF) are major cardiovascular conditions that often coexist with complex bi-directional interactions requiring specific recognition and management.\textsuperscript{1, 2} HF can cause atrial or ventricular arrhythmia through electrophysiological and structural remodeling and uncontrolled arrhythmia can produce significant left ventricular (LV) dysfunction commonly termed arrhythmia-induced cardiomyopathy (AIC). AIC is also commonly called “tachycardiomyopathy”, “tachycardia-induced cardiomyopathy” and “tachycardia-associated cardiomyopathy”, but tachycardia may not be an absolute requirement as discussed below. Although the first case of AIC was described over a century ago,\textsuperscript{3} much remains to be learned. Here, we aim to summarize the current understanding of underlying pathophysiological mechanisms, discuss the clinical implications and offer a general approach to the management of AIC, with a particular focus on AIC associated with atrial fibrillation (AF).

DEFINITION

AIC involves a triad of 1) uncontrolled arrhythmia, 2) LV dysfunction and 3) partial or complete LV functional recovery following successful arrhythmia treatment. There are no consensual precise criteria regarding the extent of LV dysfunction and no definition of LV recovery. While AIC classically causes systolic dysfunction, HF with preserved ejection fraction is also commonly associated with AF\textsuperscript{2} and a contribution to diastolic dysfunction cannot be excluded. While some suggest that diagnosing AIC requires the absence of underlying heart disease,\textsuperscript{4} we feel that this requirement is inappropriate particularly in the light of recent evidence of important LV-function improvement in HF-patients after successful AF-ablation. We prefer a broader definition that classifies AIC into two categories according to whether LV-dysfunction is caused by arrhythmia as the primary etiological factor in an otherwise normal heart, or arrhythmia precipitates/worsens HF when superimposed on pre-existing cardiac abnormalities (constituting a secondary etiological factor).\textsuperscript{5}
EPIDEMIOLOGY

AF is present in 10 to 50% of patients with HF and its prevalence increases with advancing severity of HF.\textsuperscript{1, 6} The precise proportion having AIC remains poorly defined. The prevalence of AIC may be as high as 25-50% among patients with AF and LV dysfunction undergoing atrioventricular node (AVN) ablation.\textsuperscript{7} Among patients undergoing catheter ablation for focal atrial tachycardia, the prevalence of AIC was 10%.\textsuperscript{8} A study of 625 patients undergoing arrhythmia-ablation identified AIC in 2.7%.\textsuperscript{9} A wide variety of arrhythmias have been implicated in AIC (Table 1), with AF being the most common.

PATHOPHYSIOLOGY AND MECHANISMS

The first animal model of cardiomyopathy induced by rapid pacing was described in 1962.\textsuperscript{10} Since then, this model has been widely used to study both AIC and HF.

Insights from Experimental Models

Because of space limitations, we will deal here selectively with major conceptual aspects; the reader is referred to detailed review articles focusing on the experimental literature for more information.\textsuperscript{11, 12} Figure 1 illustrates the main general mechanisms leading to AIC. Very rapid ventricular rates increase cardiac metabolic demands and impair hemodynamics; ventricular dyssynchrony reduces pump efficiency, which in itself worsens hemodynamics. These stressors do not immediately impair the intrinsic contractile function of cardiomyocytes, but lead to a cascade of mechanisms which, while initially adaptive, end up producing negative consequences. Cardiomyocytes undergo a wide range of maladaptive reprogramming and develop impaired contractile function. Evolving contractile dysfunction, in conjunction with the initial stressor(s), leads to a further hemodynamic impairment and a progressive HF syndrome. In addition,
progressive chamber dilation occurs, often causing functional atrioventricular (AV) valve regurgitation, which further impairs contractile function and hemodynamics as well as directly elevating venous pressures and worsening the HF syndrome. In parallel, the signaling pathways caused by hemodynamic and metabolic impairment cause electrophysiological derangements that lead to ventricular tachyarrhythmias and sudden death. Furthermore, AIC-induced electrical abnormalities impair impulse propagation in the heart, worsening dyssynchrony.

The black box representing maladaptive remodeling processes in Figure 1 is filled in for Figure 2. Impaired hemodynamics decrease effective coronary blood flow and, in combination with increased metabolic demands, create a mismatch between oxygen/blood flow availability and demands. Major changes result in metabolism and in the expression of genes encoding metabolic proteins. Oxidant stress results from the metabolic consequences of supply-demand mismatch, activating Ca\(^{2+}\)/calmodulin-kinase II (CaMKII) and producing major changes in cellular Ca\(^{2+}\)-handling. Neurohumoral responses, including stimulation of the adrenergic, renin-angiotensin-aldosterone and endothelin pathways, result from impaired hemodynamics and supply-demand mismatch, and along with metabolic dysfunction activate a wide range of maladaptive cell-signaling pathways and responses resulting in apoptotic and necrotic cell-death, fibrosis, and ion-channel/ion-transporter remodeling. Cell-death causes a loss of contracting myocardium and fibrosis increases myocardial stiffness, contributing to contractile dysfunction and, in association with maladaptive signaling that causes salt and water retention, produce chamber dilation that can induce functional AV-valve regurgitation, further impairing hemodynamic performance. The electrophysiological consequences of Ca\(^{2+}\)-mishandling, ion-channel/transporter remodeling and tissue fibrosis cause an arrhythmogenic environment that promotes potentially life-threatening ventricular arrhythmias and the progression of the AF-substrate, while producing conduction abnormalities that contribute to dyssynchrony. It is clear that there are positive feedback mechanisms between the primary consequences of tachycardia and
dyssynchrony and dyssynchrony/impaired hemodynamics, such that it becomes critical to effectively interrupt the vicious cycle by correcting the prime initiators (tachycardia and dyssynchrony) and interfering with maladaptive signaling.

Ventricular tachypacing has been used extensively in animal models to create tachycardiomyopathies due to both rapid heart rates and ventricular dyssynchrony. The mechanisms linking tachycardia to ventricular dysfunction have been poorly characterized. Figure 3 shows previously-unpublished data from a series of dogs subjected to ventricular tachypacing for varying periods up to 5 weeks. Of note, two clear time-courses are evident. LV-function, as reflected by LV ejection fraction (measured during sinus rhythm at comparable rates at all time-points), decreases rapidly to steady-state, within 24 hours. This change coincides with a decrease in the cellular Ca$^{2+}$-transient (measured by microfluorometry with Indo1-AM) and the caffeine-induced Ca$^{2+}$-transient, reflecting sarcoplasmic-reticulum Ca$^{2+}$-stores. Decreased Ca$^{2+}$-stores reduce the Ca$^{2+}$-transient; a reduced Ca$^{2+}$-transient decreases contractility and translates into a reduced LVEF. These data suggest that Ca$^{2+}$-mishandling is a primary and early event (indicated by blue arrows in the figure) that is crucial for contractile dysfunction. On the other hand, LV-dilation, action-potential and refractory-period prolongation (the latter two closely-linked changes reflecting ion-channel remodeling) are later events (indicated by red arrows in the figure). Their delayed occurrence suggests that they are secondary consequences, likely due to the cumulative effects of salt and water retention and ion-channel remodeling, caused by gene-reprogramming related to maladaptive signaling. Improved understanding of the primary Ca$^{2+}$-dependent processes in AIC may permit the development of novel mechanistically-driven therapeutic approaches.

It should be appreciated that the animal models of tachycardiomyopathy use extremely rapid rates (typically up to 240 bpm) to induce HF over a relatively short time frame. While these models induce progressive and severe HF, they cause only limited LV-fibrosis. Continuous tachypacing at very high rates is needed to induce HF in animal models, with near-complete reversal occurring within a couple of days after pacing-cessation, consistent with the clinical
observation that sustained tachyarrhythmias are associated with much more severe LV-dysfunction than intermittent tachyarrhythmias.  

**Clinical Aspects**

The development of AIC is mediated by complex interactions between various arrhythmia and patient characteristics (Figure 4), discussed further below. It must be recognized that the diagnosis of AIC and the determination of the causative role of the arrhythmia can be difficult. In many cases, arrhythmia contributes to HF but is not the sole cause and underlying conditions may lead to eventual return and exacerbation of HF after an initially positive response to arrhythmia control. Furthermore, even reversal of a HF syndrome upon arrhythmia management is not a definitive proof of causation, because cardiomyopathies may improve spontaneously. In addition, it is clear that factors other than arrhythmia burden and characteristics contribute to the occurrence of AIC (as illustrated in Figure 4 and discussed below), because for a given AF/heart-rate or PVC burden some patients have significant HF and others none. A variety of patient-related components, including pre-existing heart disease, systemic conditions (e.g. hypertension, neuroendocrine abnormalities) and likely genetic factors contribute to the severity and consequences of AIC.

**Arrhythmia Characteristics**

**Heart Rate**

Faster rates are associated with lower LVEF\(^{20}\), but no clear threshold has been identified. Even though the best-recognized characteristic associated with AIC is a rapid heart rate, tachycardia rate is not the only property governing the occurrence and manifestations of AIC. Ventricular dyssynchrony is also important, particularly for PVC-related cardiomyopathy. In addition, the degree of rhythm irregularity may be a contributor. \(^{22}\)
Arrhythmia burden

The arrhythmia burden is important in the development of AIC. Animal models have established that 1) the longer the rapid rate persists, the further the LV dysfunction and HF-state deteriorates, and 2) incessant arrhythmias are associated with worse hemodynamic consequences than intermittent arrhythmias.\textsuperscript{19, 21} In a cohort of patients with atrial tachycardia, incessant or very frequent paroxysmal arrhythmia was strongly associated with AIC.\textsuperscript{8} In the case of PVC-induced cardiomyopathy, the absolute number of PVCs per day and the overall burden are inversely related to the LVEF and directly related to indices of LV end-diastolic volume (LVEDV).\textsuperscript{23-25} Different cut-off values have been identified for the PVC burden above which LV dysfunction is likely to develop, varying between 16% and 24%.\textsuperscript{26, 27}

Irregularity

Rhythm irregularity is also thought to contribute to the pathophysiology of AIC, as evidenced from treatment studies of AF. In patients with moderate LV systolic dysfunction and permanent AF with acceptable ventricular rate (defined as <100 bpm), AVN ablation with pacemaker implantation nevertheless results in significant LVEF improvement.\textsuperscript{28} The same phenomenon has been observed following AF ablation.\textsuperscript{29, 30} This observation may be due to the rhythm irregularity inherent to AF, although other factors (such as the possibility that “acceptable” rates may be too rapid for a given patient) may also be involved. Atrial and ventricular ectopy are other causes of R-R variability.

Abnormal ventricular activation

Animal models have demonstrated that both atrial and ventricular rapid pacing can induce LV dysfunction but ventricular pacing seems to have a greater impact in producing LV remodeling and dysfunction.\textsuperscript{31} This observation likely reflects the added role of dyssynchrony caused by abnormal ventricular activation in AIC pathophysiology. Dyssynchrony reduces the efficiency of myocardial contraction, leading to greater LV remodeling and dysfunction. High
PVC burden\textsuperscript{23-27} and chronic right ventricular pacing\textsuperscript{32, 33} are common causes of abnormal ventricular activation-induced cardiomyopathy, even if not associated with tachycardia. PVCs with a QRS length >150 ms or with an epicardial origin are independent factors that contribute to LV dysfunction, probably through a greater degree of dyssynchronous contraction.\textsuperscript{34, 35} Left bundle branch block (LBBB)\textsuperscript{36, 37} and pre-excitation\textsuperscript{38, 39} are other conditions for which abnormal ventricular activation leading to LV dysfunction have been described.

**Patient Characteristics**

Besides arrhythmia properties, patient characteristics are important contributors to AIC occurrence and manifestations.

**Underlying cardiac comorbidities**

The presence and severity of underlying heart disease may affect the extent and the time course of AIC. Patients with pre-existing heart disease might be more sensitive to LV-function deterioration caused by a superimposed AIC. AIC may either precipitate the occurrence of HF or aggravate an already established HF condition. Although the concept seems intuitive, it remains to be formally demonstrated that the same arrhythmic insult results in greater deterioration of systolic function in patients with pre-existing cardiac dysfunction compared to those with apparently normal hearts prior to arrhythmia onset. Nonetheless, pre-existing cardiac disease does not preclude the reversibility of clinical AIC after appropriate arrhythmia management.\textsuperscript{40}

**Promptness of Medical Attention**

Arrhythmia symptomatology is an indirect determinant of AIC, in that patients that are symptomatic with their arrhythmia will seek medical attention sooner than asymptomatic ones, allowing less time for AIC to develop. Two retrospectives studies reported that the absence of symptoms was an independent predictor for PVC-induced cardiomyopathy.\textsuperscript{27, 41} A cohort of patients with focal atrial tachycardia showed that a slower ventricular rate was associated
with a lower LVEF. This apparent paradox might be explained by the fact that slower arrhythmias are more likely to be asymptomatic and therefore less likely to be treated promptly.

**Genetic predisposition**

Genetic predisposition might also have a role in the development of AIC. It has been reported that an increased serum level of angiotensin-converting enzyme (ACE) caused by a gene polymorphism is more common in a cohort of AIC compared with a cohort of patients with atrial tachyarrhythmia with normal LVEF. Pathogenic variants in the atrial-specific myosin light chain gene \textit{MYL4} can alter the contractile properties of the atrial myocyte and have been linked to early-onset AF, leading to the view that some AF cases may in fact reflect an atrial cardiomyopathy. AF is associated with gene-variants that also cause ventricular cardiomyopathies. Thus, it is possible that cardiomyopathy-causing genetic variants may underlie a subset of AF cases prone to AIC due to subclinical ventricular dysfunction. In support of the concept that acquired cardiomyopathies may have a genetic component, Ware et al demonstrated that 15% of postpartum cardiomyopathy (PPCM) cases carry truncating, likely pathogenic, dilated cardiomyopathy (DCM)-causing genetic variants. The mechanism of PPCM has been studied extensively and involves increased oxidative stress that triggers cleavage of prolactin into a deleterious anti-angiogenic and pro-apoptotic fragment resulting in impaired cardiomyocyte metabolism and ventricular dysfunction. It is therefore now accepted that DCM-associated mutations have a role in PPCM development. Analogously, although the cellular mechanisms of AIC have been described, DCM-associated mutations may well convey susceptibility to AIC development, a hypothesis that needs to be tested in the future.

**Persistent structural remodelling**

Even though systolic function normalises after successful arrhythmia treatment, diastolic dysfunction seems to persist for a longer period of time and
LVEDV remains mildly enlarged. In a study of patients with successfully ablated incessant focal atrial tachycardias and matched controls evaluated for LV function and remodeling by means of transthoracic echocardiography (TTE) and cardiac magnetic resonance imaging (MRI), persistent long-term abnormalities were noted. Five years after ablation and despite LVEF normalisation, AIC patients still had lower LV global longitudinal strain (GLS) on TTE and larger indexed LV volumes on MRI compared to controls. MRI also revealed the presence of diffuse LV fibrosis, consistent with prior experimental data indicating poor reversibility of fibrosis caused by tachycardiomyopathy. Lack of reversibility in the clinical cohort might be the result of irreversible arrhythmia-induced damage or reflect a pre-existing subclinical cardiomyopathy.

**CLINICAL PRESENTATION**

The clinical presentation of AIC is variable but usually involves LV systolic dysfunction with or without HF symptoms. The causative arrhythmia, which must in theory precede the appearance of cardiomyopathy, may not always be present when HF is first diagnosed. Care must therefore be taken to adequately search for subclinical arrhythmia when LV dysfunction is discovered de novo in a patient. Conversely, patients may seek medical attention for arrhythmia symptoms, with sub-clinical LV dysfunction, which can sometimes be severe, being discovered incidentally.

Sudden cardiac death (SCD) is associated with any form of advanced HF, but the specific risk of SCD in the context of AIC remains poorly defined. Rapid pacing-induced cardiomyopathy is associated with delayed ventricular repolarisation in animal models, as well as ventricular arrhythmia and sudden death. A few studies have noted the risk of SCD in the AIC population, even when the primary arrhythmia has been treated appropriately and LV function has "normalised". The persistent cardiac structural remodeling described above might serve as a favorable substrate for ventricular arrhythmogenesis and SCD,
just as persistent atrial fibrosis post-rhythm normalization leaves a substrate for AF maintenance.\textsuperscript{48}

**DIAGNOSIS: CAN WE PREDICT THE RESPONSE OF LV DYSFUNCTION TO ARRHYTHMIA CONTROL?**

When a patient presents concurrently with arrhythmia and HF, one of the greatest challenges is to elucidate which preceded the other and is the primary causative factor. Predicting the recovery of LV dysfunction after adequate arrhythmia control would permit an upstream diagnosis of AIC, allowing the clinician to treat the patient’s cardiomyopathy with a more aggressive anti-arrhythmic approach.

Sometimes, the relative timing of arrhythmia and HF occurrence can provide a clear clue regarding the primary etiology of the arrhythmia-HF association. In clinical practice, making such a distinction is often quite difficult. In the Framingham Heart Study, 21\% of the individuals having AF and HF had both conditions diagnosed on the same day.\textsuperscript{55} A component of AIC should be suspected whenever LV dysfunction is out of proportion to the extent of underlying heart disease.

Although there is no initial imaging or biochemical parameter that can definitively distinguish AIC from other forms of non-ischemic DCM, several markers have been identified that help to predict significant LV functional recovery after adequate arrhythmia control (Table 2). AIC patients present with smaller LV cavities compared to those with DCM and concomitant arrhythmia.\textsuperscript{56, 57} Early right ventricular systolic dysfunction on MRI is also suggestive of AIC.\textsuperscript{58} A recent study by Kusunose et al\textsuperscript{59} demonstrated the potential value of longitudinal strain (LS) using echocardiographic speckle tracking in predicting LV functional recovery in patients with suspected AIC. At baseline, patients with AIC had a more profound decrease in apical LS compared to the mid and basal segments, while patients with persistent LV dysfunction after arrhythmia correction had a
predominant reduction of LS in the basal segments. Thus, the relative apical LS ratio (RALS R: average apical LS / [average basal LS + average mid LS]) might be useful to predict LV functional recovery: in the Kusunose study, the association with outcome was excellent.\textsuperscript{59} A study of patients with LV dysfunction and rapid AF or atrial flutter treated with cardioversion analyzed the NT-proBNP concentration in samples obtained at baseline and subsequent follow-up post cardioversion.\textsuperscript{60} The authors found that a NT-proBNP ratio >2.3 (NT-proBNP baseline/NT-proBNP week 1) was strongly associated with LV functional recovery, implying that AIC shows a more rapid NT-proBNP decline after adequate arrhythmia treatment compared with other causes of cardiomyopathy.

An analysis of endomyocardial biopsies among 189 patients with non-ischemic new-onset HF, with 19 of them retrospectively identified as AIC, has recently been reported.\textsuperscript{61} AIC cases were compared to 91 patients with inflammatory cardiomyopathy and to 79 with DCM. The authors found that LV biopsies from AIC cases showed greater expression of major histocompatibility complex class II and more infiltration with CD68 macrophages compared with DCM. Mitochondria were abnormally distributed near the intercalated disks compared to healthy subjects. The authors also showed the presence of myocardial fibrosis in AIC, albeit less than in inflammatory cardiomyopathy and DCM.

**MANAGEMENT**

New-onset HF should prompt an etiology-directed investigation to identify reversible causes. Clinicians should maintain a high index of suspicion for AIC because it can often be subtle and superimposed on another heart disease, and because it is one of the few clearly reversible causes of DCM. The causative arrhythmia may not always be present when HF is first diagnosed, and prolonged electrocardiographic monitoring is sometimes needed. Management should always include attention to both the underlying arrhythmia and standard HF treatment according to established guidelines.\textsuperscript{2, 62} Considering the potential
reversibility of AIC, any suspicion of its involvement should prompt aggressive treatment of documented arrhythmias.

Even though HF symptoms often completely resolve following arrhythmia treatment and LV function improvement, effort should be made to maintain long-term control of the causative arrhythmia. Relapses may be associated with rapid LVEF decline and major adverse events.\textsuperscript{52}

**AF-induced Cardiomyopathy**

Management of AF in patients with HF is the subject of a specific review in this issue of the *Journal*.\textsuperscript{53} We will thus focus our discussion on aspects specific to AF-induced cardiomyopathy. Most of the available studies in the literature included AIC patients along with the general HF and AF populations, without distinguishing the underlying HF etiology. In most randomized studies comparing different approaches to AF management, the LVEF improvement observed in more aggressive treatment groups suggest the presence of a certain degree of AIC (Table 3). Several options are available to treat AF in the HF population. The main dilemma resides in choosing between a rate versus rhythm control approach, with both strategies having invasive and non-invasive/pharmacological options. A suggested clinical approach to the diagnosis and management of suspected AF-induced cardiomyopathy is depicted in Figure 5.

Pharmacological rhythm versus rate control therapies are often considered equivalent strategies in HF with respect to clinical outcomes.\textsuperscript{64} In the AF-CHF trial,\textsuperscript{65} 1376 patients with AF, HF and a LVEF ≤35% were randomised to either pharmacological rhythm (mainly amiodarone) or rate control therapy. After a mean follow-up of 37 months, there was no difference between groups in cardiovascular mortality. In an AF-CHF substudy, both rhythm- and rate-control groups showed significant improvement of LVEF (8% vs 4.5%; absolute differences); there was a trend towards greater improvement with rhythm control, but statistical significance was not reached.\textsuperscript{40} The smaller CAFE-II trial had a
similar design and reported greater LV function improvement with rhythm control.\textsuperscript{66} Controversy still remains as to whether the adverse effects associated with anti-arrhythmic drug medication may counter-balance the beneficial consequences of maintaining sinus rhythm.\textsuperscript{67, 68}

When considering an invasive rate control approach for refractory AF, the “pace and ablate” strategy with AVN ablation and RV pacing is a potential option. Although it leaves the patient pacemaker-dependent, improved clinical outcomes and LVEF have been shown.\textsuperscript{69} Because of the deleterious effects of chronic RV pacing, cardiac resynchronisation therapy (CRT) should be considered in HF/LV dysfunction patients requiring permanent pacemaker implantation.\textsuperscript{70, 71}

The PABA-CHF study\textsuperscript{72} randomised 81 patients with AF and HF with LVEF \(\leq 40\%\) to either catheter ablation of AF or AVN ablation with biventricular pacing. At 6 months, patients in the AF-ablation group had greater LVEF improvement compared with patients undergoing AVN ablation with biventricular pacing (8\% vs -1\%; absolute changes, \(p<0.001\)). Patients had adequate rate-control at baseline and the majority had coronary artery disease. A retrospective study compared outcomes among patients with DCM and ischemic heart disease following AVN ablation with biventricular pacing.\textsuperscript{73} All patients had poorly controlled permanent AF and a LVEF <35\%. LVEF increased significantly in the DCM cohort compared to the ischemic CMP cohort (11.2\% vs 0.5\% \(p<0.01\)). This finding suggests, not surprisingly, that the prevalence of unrecognized AIC is higher among the DCM population than the ischemic heart disease population.

The ARC-HF\textsuperscript{74} and the CAMTAF\textsuperscript{75} randomised trials compared rhythm control with AF catheter ablation to pharmacological rate control. Both reported high ablation success-rates with 88\% freedom from AF at 12 months for ARC-HF and 81\% at 6 months for CAMTAF. In ARC-AF, both the ablation arm and the rate control arm showed statistically significant LV function improvement, with a trend towards greater improvement in the ablation group (10.9\% vs. 5.4\%).
p=0.055). Non-optimal rate control at trial baseline might explain the substantial improvement in the medical group. With both groups having adequate rate control at enrolment, the CAMTAF trial showed significant LVEF improvement in the catheter ablation arm compared to the medical therapy arm (8.1% vs -3.6% p<0.001). Another similar trial did not demonstrate any difference in LV functional improvement between catheter ablation and medical rate control, but the procedural success rate was significantly lower with 50% freedom of AF at 6 months. The AATAC\textsuperscript{77} trial randomised 203 patients with persistent AF and HF with LVEF\leq40\% to receive AF catheter ablation or amiodarone treatment. After a minimum of 24 months follow-up, the catheter ablation group showed superior sinus rhythm maintenance versus the amiodarone group (70\% vs 34\% p<0.001) and demonstrated greater improvements in LVEF (8.1\% vs 6.2\% p=0.02). The CAMERA-MRI trial\textsuperscript{78} randomised 68 patients with persistent AF and HF with LVEF\leq45\% to either AF catheter ablation or pharmacological rate control therapy. At 6 months, LVEF improved significantly more in the catheter ablation compared to the medical group (18.3\% vs 4.4\% p<0.0001). Interestingly, only patients with idiopathic cardiomyopathy were included, which might partially explain the marked improvement in LVEF in the catheter ablation group because an unknown (and possibly significant) number of patients with AIC might have been included. More recently, the CASTLE-AF\textsuperscript{79} trial showed a significantly lower composite end-point of mortality and hospitalization for HF among patients with AF and HF with LVEF\leq35\% who were randomised to AF catheter ablation compared to medical treatment (either rate or rhythm control). LVEF also improved to a greater extent in the catheter ablation group (8.0\% vs 0.2\% p=0.005). The RAFT-AF trial is still in progress and should complement our understanding of LV recovery after AF treatment through catheter ablation.

The previously discussed trials do not focus on an AIC population specifically. It should be noted that the evidence available from these trials is far from conclusive because of their non-blinded nature, potential spontaneous
changes in the severity of the HF syndrome and underlying cardiomyopathies, and the possible contributions of non-antiarrhythmic therapies.

In addition to the prospective studies that did not select for AIC listed in Table 3, small studies restricted to AIC patients also suggest better LVEF recovery with rhythm control. Identifying patients with heart failure with reduced ejection fraction (HFrEF) and concomitant AF that would benefit from AF ablation remains challenging. Quantifying LV myocardial fibrosis before attempting treatment with catheter ablation might be useful, as a smaller burden of late gadolinium enhancement on cardiac MRI seems to be associated with greater LVEF recovery. Testing for LV functional recovery with a short term of antiarrhythmic medication or an electrical cardioversion before the ablation could be another strategy to clarify the potential benefits of such a procedure.

**Cardiomyopathy associated with other supraventricular arrhythmias**

Atrial flutter is generally more difficult to control pharmacologically than AF, but on the other hand is more susceptible to permanent cure with ablation. Rhythm control is often the first-choice approach to rhythm management in atrial flutter because of the difficulty of achieving adequate rate control. Given its high procedural success and its low rate of complications, curative catheter ablation for symptomatic patients with typical flutter is recommended first-line therapy. Although less frequent, supraventricular tachycardia can also induce cardiomyopathy and sinus rhythm maintenance should be targeted in such individuals. While either pharmacological arrhythmia suppression or catheter ablation are possible, catheter ablation should be favoured for recurrent arrhythmia because of its very high long-term success rate.

**PVC-induced cardiomyopathy**
Pharmacological therapy with beta-blocker is a reasonable first choice to PVC-induced cardiomyopathy treatment despite modest efficacy. The CHF-STAT\textsuperscript{86} trial demonstrated that amiodarone is effective at decreasing PVC burden and improving LVEF among a HF population with LVEF $\leq 40\%$ and $\geq 10$ PVCs per hour. However, amiodarone use is often limited by long-term adverse effects. A cohort of 1185 patients with PVCs treated with catheter ablation showed a procedural success rate (defined as $\geq 80\%$ PVC reduction) of 71$\%$ at 1.9 years.\textsuperscript{35} Among these, 245 patients had LVEF $< 50\%$ before the ablation. Post-intervention, their mean ejection fraction increased from 38$\%$ to 50$\%$ and their global PVC burden decreased from 27$\%$ to 5$\%$. Two studies reported significant LVEF recovery with a 80$\%$ PVC reduction, which suggest that the therapeutic goal should not necessarily be complete arrhythmia suppression.\textsuperscript{87, 88}

**Sudden cardiac death prevention**

Given the reported risk of SCD in AIC,\textsuperscript{52-54} implantable cardioverter defibrillator (ICD) use may be considered. The approach to SCD prevention among the AIC population is not covered specifically by current guidelines. While awaiting more literature, we apply non-ischemic cardiomyopathy primary prevention algorithms in AIC.\textsuperscript{89, 90}

**Termination of medical therapy**

According to the current Canadian Guidelines for the Management of HF, an attempt at stepwise withdrawal of HF therapy might be justified under certain circumstances.\textsuperscript{2} To consider HF therapy withdrawal, the patient must be asymptomatic and LV size and function must have normalized. For AIC, arrhythmia should be well controlled before considering withdrawal of medical HF therapy.\textsuperscript{2} Very close patient follow-up with ambulatory electrocardiographic monitoring and cardiac imaging is indicated in AIC patients, given the evidence pointing towards possible irreversible myocardial damage and risk of recurrence. Patients should also be instructed to recognize symptoms of arrhythmia and HF.
CONCLUSIONS

AIC is a common entity with variable clinical presentations. The development of AIC depends on inter-related patient and arrhythmia factors. Treatment strategies are rapidly evolving, with increasing evidence pointing to the superiority of catheter ablation for many patients. The prediction of cardiac recovery in patients with coincident HF and arrhythmia, as well as patient selection for interventional therapy, remain major challenges. Further research is needed to improve our understanding of the pathophysiologic determinants of AIC, including genetic factors.

Acknowledgments
The authors thank Jennifer Bacchi for secretarial help with the manuscript.

Funding Sources
Rafik Tadros is supported by the Philippa and Marvin Carsley Chair in cardiology, Fonds de la recherche du Quebec en santé and an operating grant from the Canadian Cardiovascular Society (CCS-AF award). Stanley Nattel is supported by a Foundation Award from the Canadian Institutes of Health Research and operating grants from the Heart and Stroke Foundation of Canada. Reza Wakili was supported by the German Centre for Cardiovascular Research (DZHK), European Union’s Horizon 2020 Research and Innovation Program and the Deutsche Forschungsgemeinschaft (DO 637/23-1; Projektummer 394433254).

Disclosures
None.
REFERENCES


Table 1. Potential Causes of Arrhythmia-Induced Cardiomyopathy

<table>
<thead>
<tr>
<th>Supraventricular arrhythmia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Atrial flutter</td>
</tr>
<tr>
<td>Atrial tachycardia</td>
</tr>
<tr>
<td>Atrioventricular nodal reentrant tachycardia</td>
</tr>
<tr>
<td>Atrioventricular reentrant tachycardia</td>
</tr>
<tr>
<td>Permanent junctional reciprocating tachycardia</td>
</tr>
<tr>
<td>Premature atrial contractions</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
</tr>
<tr>
<td>Premature ventricular contractions</td>
</tr>
</tbody>
</table>
Table 2. Markers associated with LV function recovery reflecting a component of AIC following successful arrhythmia treatment.

<table>
<thead>
<tr>
<th>Markers</th>
<th>Favor AIC</th>
<th>Favor DCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD(^{56, 57})</td>
<td>Lesser dilatation</td>
<td>Greater dilatation</td>
</tr>
<tr>
<td>RV dysfunction(^{58})</td>
<td>Earlier involvement</td>
<td>Later involvement</td>
</tr>
<tr>
<td>Strain distribution(^{59})</td>
<td>Decreased apical strain</td>
<td>Preserved apical strain</td>
</tr>
<tr>
<td></td>
<td>Smaller RALSR</td>
<td>Greater RALSR</td>
</tr>
<tr>
<td>NT-proBNP following cardioversion(^{60})</td>
<td>Rapid NT-proBNP decrease</td>
<td>Slow or limited NT-proBNP decrease</td>
</tr>
<tr>
<td>Histopathology(^{61})</td>
<td>Greater MHC II</td>
<td>Lesser MHC II</td>
</tr>
<tr>
<td></td>
<td>Greater CD68 infiltration</td>
<td>Lesser CD68 infiltration</td>
</tr>
<tr>
<td></td>
<td>Presence of EMID sign</td>
<td>Absence of EMID sign</td>
</tr>
<tr>
<td></td>
<td>Lesser degree of fibrosis</td>
<td>Greater degree of fibrosis</td>
</tr>
</tbody>
</table>

AIC, Arrhythmia-induced cardiomyopathy; DCM, Dilated cardiomyopathy; LVEDD, Left ventricular end-diastolic diameter; RV, Right ventricular; RALSR, Relative apical longitudinal strain ratio; MHC, Major histocompatibility complex; EMID, Enhancement of mitochondria at the intercalated discs.
Table 3. Major randomised controlled trials comparing treatment strategies for AF patients with HFrEF.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Year</th>
<th>N</th>
<th>Compared therapy</th>
<th>Follow-up</th>
<th>Primary outcome</th>
<th>Freedom from AF</th>
<th>Δ LVEF from baseline</th>
<th>p-value (Δ LVEF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Rhythm vs Medical Rate control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF-CHF&lt;sup&gt;nr&lt;/sup&gt;,&lt;sup&gt;1&lt;/sup&gt; Roy et al.</td>
<td>2008</td>
<td>1376</td>
<td>Rhythm vs Rate control</td>
<td>37 months</td>
<td>Cardiovascular mortality</td>
<td>73% vs ≠35%</td>
<td>8.0% vs 4.5%</td>
<td>p=0.19</td>
</tr>
<tr>
<td>CAFE-II&lt;sup&gt;nr&lt;/sup&gt; Shelton et al.</td>
<td>2009</td>
<td>61</td>
<td>Rhythm vs Rate control</td>
<td>12 months</td>
<td>QoL</td>
<td>66% vs 0%</td>
<td>Qualitative increase vs no increase in LVEF</td>
<td>p=0.014</td>
</tr>
<tr>
<td>Invasive Rhythm vs Invasive Rate control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PABA-CHF&lt;sup&gt;nr&lt;/sup&gt;,&lt;sup&gt;2&lt;/sup&gt; Khan et al.</td>
<td>2008</td>
<td>81</td>
<td>RF catheter ablation vs AVN ablation + CRT</td>
<td>6 months</td>
<td>LVEF, 6MWT and QoL</td>
<td>88% vs 0%</td>
<td>8.0% vs -1.0%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Invasive Rhythm vs Medical treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MacDonald et al.&lt;sup&gt;3&lt;/sup&gt;</td>
<td>2010</td>
<td>41</td>
<td>RF catheter ablation vs Rate control</td>
<td>6 months</td>
<td>Change in LVEF</td>
<td>50% vs 0%</td>
<td>4.5% vs 2.8% (MRI) 8.2% vs 1.4% (RNVG)</td>
<td>p=0.6 p=0.032</td>
</tr>
<tr>
<td>ARC-HF&lt;sup&gt;nr&lt;/sup&gt;,&lt;sup&gt;2&lt;/sup&gt; Jones et al.</td>
<td>2013</td>
<td>52</td>
<td>RF catheter ablation vs Rate control</td>
<td>12 months</td>
<td>Peak VO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>88% vs 4%</td>
<td>10.9% vs 5.4%</td>
<td>p=0.055</td>
</tr>
<tr>
<td>CAMTAF&lt;sup&gt;nr&lt;/sup&gt;,&lt;sup&gt;2&lt;/sup&gt; Hunter et al.</td>
<td>2014</td>
<td>50</td>
<td>RF catheter ablation vs Rate control</td>
<td>6 months</td>
<td>Difference in LVEF</td>
<td>81% vs 0%</td>
<td>8.1% vs -3.6%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>AATAC&lt;sup&gt;nr&lt;/sup&gt; Di Biase et al.</td>
<td>2016</td>
<td>203</td>
<td>RF catheter ablation vs Amiodarone</td>
<td>24 months</td>
<td>Freedom from AF</td>
<td>70% vs 34%</td>
<td>8.1% vs 6.2%</td>
<td>p=0.02</td>
</tr>
<tr>
<td>CAMERA-MRI&lt;sup&gt;nr&lt;/sup&gt;,&lt;sup&gt;2&lt;/sup&gt; Prabhu et al.</td>
<td>2017</td>
<td>68</td>
<td>RF catheter ablation vs Rate control</td>
<td>6 months</td>
<td>Change in LVEF</td>
<td>75% vs 0% (at 1 month)</td>
<td>18.3% vs 4.4%</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>CASTLE-AF&lt;sup&gt;nr&lt;/sup&gt;,&lt;sup&gt;2&lt;/sup&gt; Marrouche et al.</td>
<td>2018</td>
<td>363</td>
<td>RF catheter ablation vs Medical therapy</td>
<td>38 months</td>
<td>Mortality and Hospitalization for HF</td>
<td>63.1% vs 21.7%</td>
<td>8.0% vs 0.2%</td>
<td>p=0.005</td>
</tr>
</tbody>
</table>
AF, Atrial fibrillation; CRT, cardiac resynchronization therapy; HFrEF, Heart failure with reduced ejection fraction; LVEF, Left ventricular ejection fraction; QoL, Quality of life; RF, Radiofrequency; 6MWT, 6 minutes walk test; MRI, Magnetic resonance imaging; RNVG = radionuclide ventriculography; VO₂ = Oxygen consumption
Figure 1. A schematic diagram of the mechanisms linking tachycardia and dyssynchrony, the principle inducers of AIC (red font), to the principal clinical outcomes, the heart failure syndrome and arrhythmias with risk of sudden death (red font in boxes). Tachycardia and dyssynchrony lead to increased metabolic demands and impaired hemodynamics, the principle derangements that initiate downstream maladaptive signaling. A complex set of maladaptive signaling processes (represented here by a block dashed box) result in reprogramming of cardiomyocyte gene-expression and contractile impairment and adverse electrophysiological remodeling. Contractile dysfunction ultimately results in the HF Syndrome and electrophysiological cause malignant arrhythmias and conduction abnormalities. Adverse feedback loops result from functional AV-valve regurgitation, which enhances hemodynamic dysfunction and the HF manifestations and conduction abnormalities that cause or aggravate dyssynchrony.

Figure 2. This figure revisits the primary events shown in Figure 1, filling in details in the dashed box representing key maladaptive signaling systems. The more proximal abnormalities in the mechanistic chain (in red and blue fonts) are those most effectively targeted by therapies. For more detailed discussion, see text.

Figure 3. Mean and standard error values for echocardiographic left-ventricular (LV) ejection fraction (LVEF), intracellular $\text{Ca}^{2+}$ transient amplitude upon field stimulation at 1 Hz, the amplitude of the $\text{Ca}^{2+}$ transient induced by a local bolus of 10 mM caffeine (an indicator of sarcoplasmic-reticulum $\text{Ca}^{2+}$-stores), LV diastolic volume, LV cellular action-potential duration to 90%-repolarization ($\text{APD}_{90}$), and LV effective refractory period (ERP). Dogs (n=5/group) were subjected to right-ventricular pacing at 240 bpm for 24 hrs or 1 or 2 weeks, and then 220 bpm for 3 additional weeks (5-week group) followed by in vivo hemodynamics and electrophysiology, as well as LV cell isolation and study. In addition, cellular data was obtained from 5 dogs tachypaced at 240 bpm for 12
hours. *P<0.05, **P<0.01 versus control dogs (Baseline) by one-way ANOVA with Bonferroni correction. One set of related changes occurs very early (time of stead-state shown by vertical blue arrow), another occurs much later (red arrows).

**Figure 4.** Overview of patient and arrhythmia characteristics that govern AIC development and manifestations.

**Figure 5.** Approach to the initial management of suspected AF-induced cardiomyopathy.
Figure 1

- Rapid Ventricular Rate
- Increased Metabolic Demands
- Dyssynchrony
- Impaired hemodynamics
- CHANGES CAUSING MALADAPTIVE REMODELING
  - Contractile Dysfunction
  - Chamber Dilation
  - Heart Failure Syndrome
  - AV valve regurgitation
  - Electrophysiological consequences
    - Sudden Death
    - Arrhythmias
Figure 2

- Rapid Ventricular Rate
- Increased Metabolic Demands

- Impaired hemodynamics
  - Supply-Demand Mismatch
  - Neurohormonal Response
  - Oxidant Stress
  - Metabolic Stress/Adaptation

- Maladaptive signaling pathways/Responses

- Cell Death (apoptosis, necrosis)

- Abnormal Calcium Homeostasis
- Fibrosis

- Salt and water retention

- Dyssynchrony
- Contractile Dysfunction
- Chamber Dilatation
- AV valve regurgitation

- Electrophysiological consequences

- Heart Failure Syndrome
- Arrhythmias
- Sudden Death
**Figure 3**

**A** LVEF (%)
- Baseline
- 24 h
- 1 wk
- 2 wk
- 5 wk

**B** LV diastolic vol (ml)
- Baseline
- 24 h
- 1 wk
- 2 wk
- 5 wk

**C** Ca\(^{2+}\) transient amplitude
- Baseline
- 12 h
- 24 h
- 1 wk
- 2 wk
- 5 wk

**D** LV APD
- Baseline
- 12 h
- 24 h
- 1 wk
- 2 wk
- 5 wk

**E** Caffeine-induced Ca\(^{2+}\) transient
- Baseline
- 12 h
- 24 h
- 1 wk
- 2 wk
- 5 wk

**F** LV ERP
- Baseline
- 12 h
- 24 h
- 1 wk
- 2 wk
- 5 wk
Arrhythmia-induced Cardiomyopathy

Arrhythmia Characteristics
- Heart rate
- Duration / Burden
- R-R Variability
- Abnormal ventricular activation/dyssynchrony

Patient Characteristics
- Underlying heart disease
- Promptness of presentation
- Other systemic conditions
- Genetic predisposition

Figure 4
Atrial Fibrillation and CHF with LV systolic dysfunction

Identify reversible causes and treat accordingly

Standard HFREF treatment

Suspected AIC
(Table 2)

Weak suspicion

Test LV dysfunction reversibility (i.e. cardioversion)

No LVEF improvement

Pharmacological rate control

Pharmacological rhythm control

Strong suspicion

LVEF improvement

Favour rhythm control

Invasive vs pharmacological

Favouring Ablation
- Small LA volume
- Paroxysmal AF
- Absence of comorbidities
- Anti-arrhythmic drug failure

Catheter ablation

Figure 5
学霸图书馆

www.xuebalib.com

本文献由“学霸图书馆-文献云下载”收集自网络，仅供学习交流使用。

学霸图书馆（www.xuebalib.com）是一个“整合众多图书馆数据库资源，提供一站式文献检索和下载服务”的24小时在线不限IP图书馆。

图书馆致力于便利、促进学习与科研，提供最强文献下载服务。

图书馆导航：
图书馆首页 文献云下载 图书馆入口 外文数据库大全 疑难文献辅助工具