

# TACHICARDIOMIOPATIA: COSA NASCE PRIMA, L'ARITMIA O LA CARDIOMIOPATIA?

## ARRHYTHMIAS AND CARDIOMYOPATHY: WHEN ARRHYTHMIAS COME FIRST

*I. Bonadei, V. Carubelli, E. Gorga, C. Lombardi, E. Vizzardi, M. Metra*

**Cardiology, Department of Medical and Surgical Specialties,  
Radiological Sciences and Public Health.  
University and Civil Hospital, Brescia.**

The relationship between arrhythmias and Heart Failure (HF) is bidirectional. HF is associated with tachyarrhythmias which may worsen cardiac dysfunction and, in the case of malignant ventricular arrhythmias, cause death<sup>1-3</sup>. On the other hand, there are cases in which arrhythmias come first and cause cardiac dysfunction and HF. These cases are defined as Arrhythmias Induced Cardiomyopathies (AIC) and are an important, partially or completely reversible, cause of HF. These will be the main focus of this article.

### **Definition**

AIC refers to an impairment of Left Ventricular (LV) function caused by atrial or ventricular tachyarrhythmias which is partially or completely reversible after normalization of the Heart Rate (HR). AIC are classified into two groups: one in which the tachyarrhythmias are the only cause of the myocardial dysfunction (pure or arrhythmia induced) and another in which the arrhythmia exacerbates ventricular dysfunction and HF in a patient with concomitant heart disease (impure or arrhythmia mediated)<sup>4,5</sup>.

### **Epidemiology**

AIC is a diagnosis of exclusion and therefore estimations of its incidence are limited and uncertain. AIC is likely under-diagnosed, with its true incidence being higher than reported in literature. Several studies have demonstrated that both supraventricular and ventricular tachyarrhythmias, including frequent Premature Ventricular Complexes (PVCs), can cause AIC (tab. I)<sup>4,6,7</sup>.

As an example, atrial fibrillation (AF) is the most common arrhythmia as well as the most common cause of AIC. It is estimated that up to 50% of the

Table 1 - Arrhythmias causing AIC, modified from 7.

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*Supraventricular*

- Atrial fibrillation
- Atrial flutter
- Atrial tachycardia
- Permanent junctional reciprocating tachycardia
- AV nodal reentrant tachycardia
- AV reentrant tachycardia
- Inappropriate sinus tachycardia (rare)

*Ventricular*

- Right ventricular outflow tract ventricular tachycardia
- Fascicular tachycardia
- Bundle branch reentry ventricular tachycardia

*Ectopy*

- Frequent PVCs

*Pacing*

- Persistent rapid ventricular pacing
  - High-rate atrial pacing
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patients with AF may have an at least mild impairment of LV systolic function due to AF<sup>8</sup>. In addition, AF is present in 10% to 50% of the patients with HF<sup>2,9,10</sup> and may cause a deterioration of cardiac function, clinical symptoms and poorer outcomes through multiple mechanisms, including a poor control of ventricular rate, atrial – ventricular dyssynchrony and an irregular ventricular response<sup>5,11,12</sup>. Despite its high prevalence, it is difficult to estimate to which extent AF is the cause of HF or just its epiphenomenon and, accordingly, clinical trials comparing different strategies for the treatment of AF in HF have often yielded controversial results (see below). Even frequent PVCs and/or non-sustained ventricular tachycardia may cause AIC with a prevalence of AIC of 9% to 34% among the patients referred for electrophysiological evaluation<sup>5,13</sup>.

### Pathophysiology

Experimental models have shown that rapid cardiac pacing can recapitulate the phenotype of AIC causing LV remodeling and HF in a time-dependent, highly predictable, manner<sup>5,14</sup>. Whipple and colleagues developed the first experimental model of AIC in 1962<sup>15</sup>. Further studies showed the time sequence of events during atrial or ventricular pacing and their reversibility upon pacing cessation. There are no accurate data with regards of the HR above which there is an increased risk of AIC. However, any sustained HR above 100 beats per minute seems able to cause it.

Hemodynamic changes occur as soon as 24 h after rapid pacing, with continued deterioration in ventricular function for up to 3 to 5 weeks, resulting in clinically evident HF. These changes are reversible after termination of pacing<sup>8</sup>. The earliest changes occurring during rapid cardiac pacing recapitulate LV remodeling with LV dilatation and a decrease in Ejection Fraction (EF).

They start during the first day of pacing and continue to worsen in the following weeks up to 3-5 weeks after the start. Hemodynamic impairment may be initially absent but then, by the second week, an increase in the central venous pressure, pulmonary capillary wedge pressure and systemic vascular resistance and a decrease in cardiac output can be observed, finally leading to overt HF<sup>5,8,16</sup>. A full recover of the hemodynamic changes may take up to 4 weeks after pacing cessation and LV end-diastolic and end-systolic volumes can remain above the initial values for up to 12 weeks<sup>17</sup>.

The primary mechanism leading to LV remodeling seems to be the loss of the normal myocardial extracellular matrix structure, composition and function caused by an increase of matrix metalloproteinase activity and expression<sup>5,18</sup>. These changes in the extracellular matrix seem to precede the myocyte contractile dysfunction. When cardiomyocyte function is impaired, a decreased activity and density of ryanodine-binding Ca-release channel of the sarcoplasmic reticulum with a prolongation of myocardial Ca<sup>2+</sup> transients and defects in Ca<sup>2+</sup> cycling and abnormal excitation-contraction coupling have been shown<sup>5</sup>.

The neurohormonal changes observed in AIC are similar to those of other forms of HF. In pacing-induced HF, changes in HR, atrial pressure and volume cause increased plasma ANP and BNP concentrations, which may first compensate sympathetic and renin-angiotensin-aldosterone systems activation but are then unable to do so because of depletion of atrial ANP likely due also to increased degradation by endopeptidase<sup>19</sup>.

The increase in plasma norepinephrine concentrations caused by rapid pacing are associated with abnormalities in  $\beta$ -adrenergic receptor density and cAMP and reduced myocyte  $\beta$ -adrenergic responsiveness due to the activation of both sympathetic<sup>20,21</sup> and renin-angiotensin-aldosterone systems<sup>22</sup>. Increased oxidative stress and inflammatory activation also contribute to AIC development. Thus, similarly to what described for the progression of cardiac dysfunction and HF, in general, also the progression of AIC is described by an early compensatory phase (<7 days), in which natriuretic peptides secretion prevents the development of hemodynamic abnormalities, leading to a LV dysfunction phase (1 to 3 weeks) and eventually to an overt HF phase (>3 weeks). All these phases are caused by the interplay of multiple mechanisms, including neurohormonal and inflammatory activation, and extracellular matrix and myocyte changes<sup>5</sup>.

## Management

Diagnosis (tab. II) and treatment of AIC must take into account the characteristics of the arrhythmia including its type, HR, duration, rhythm irregularity and concomitant heart disease.

AIC treatment mainly consists in HF and arrhythmia management. Continued therapy with neurohormonal antagonists (i.e. ACE inhibitors, mineralocorticoid receptors antagonists and beta-blockers) is necessary to inhibit LV remodeling. It is uncertain whether and how long neurohormonal antagonists are needed after arrhythmia cessation and regression of the LV function abnormalities<sup>23</sup>. Although an improvement in LV function can be already observed one week after the start of the arrhythmia control, full recovery of LV

*Table II* - Suggested criteria for the diagnosis of AIC, modified from 7.

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- New onset of LV dysfunction.
  - Chronic or recurrent tachycardia with HR >100 beats per minute.
  - No signs of acute coronary syndrome or other causes of non-ischemic cardiomyopathy.
  - Absence of LV hypertrophy as a possible cause of HF.
  - Normal LV dimensions.
  - Recovery of LV function after control of tachycardia within 1-6 months.
  - Rapid decline in LVEF following recurrence of tachycardia in a patient with a previous recovery of LV function after tachycardia control.
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function usually occurs after at least 3-4 months. A steep decline in LV function has been shown after recurrence of the arrhythmia, or withdrawal of the HF medications, suggesting the long-term persistence of myocardial structural abnormalities in patients with AIC. Thus, HF treatment is recommended even after the recovery of LV systolic function<sup>2</sup>. Management of some of the specific arrhythmias is shortly described below.

### ***Atrial fibrillation***

This is the most common arrhythmia and the most common cause of AIC in adults<sup>1,2</sup>. AF may cause LV dysfunction and AIC through multiple mechanisms including the loss of atrial contraction, atrial-ventricular dyssynchrony, the rapid and irregular ventricular response. Particularly, loss of atrial systole is associated with impaired LV diastolic filling, increased intra-atrial pressure, and a 20-30% stroke volume reduction. Further, persistent tachycardia can impair myocardial contractility, either directly or through increased neurohormonal activation<sup>24</sup>.

Management of AF includes prevention of thromboembolic events, rate control and rhythm control.

### ***Prevention of thromboembolic events***

With respect of the prevention of thromboembolic events, HF may cause, by itself, the indication to oral anticoagulant therapy with either Vitamin K Antagonists (VKAs) or Non-VKA Oral AntiCoagulants (NOACs)<sup>25,26</sup>. Randomized controlled trials in patients with non valvular AF have included patients with HF. Subsequent analyses and a meta-analysis have shown that single-/high-dose NOACs regimens have a better efficacy and safety, compared with VKAs, whereas low-dose regimens have similar efficacy and a tendency to less major bleeding, compared with VKAs<sup>27</sup>. Left atrial appendage occluders can be considered in the patients with contraindications to oral anticoagulants<sup>1</sup>.

### ***Rhythm control***

Randomized trials comparing a rhythm control strategy, generally based on cardioversion plus long-term amiodarone administration, with a rate control strategy have failed to show any benefit of rhythm control on all-cause and cardiovascular mortality and HF hospitalizations. Thus, there is no evidence favoring rhythm control versus rate control in patients with AF and HF<sup>2,28</sup>.

Large observational studies have, however, suggested a benefit of the rhythm control strategy on long-term mortality and stroke rates<sup>29,30</sup>. Further, the lack of benefit of the rhythm control strategy in randomized trials can be related to patients' treatment during follow-up with up to 40% of the patients in sinus rhythm in the rate control group<sup>31,32</sup>. Second, the neutral results of randomized trials seems mostly caused by the untoward effects of antiarrhythmic drugs<sup>29,32</sup>.

A rhythm control strategy based on catheter ablation with pulmonary vein isolation seems able to improve or reverse AIC and has favorable effects on LV function, quality of life and exercise capacity<sup>2,12</sup>. Pulmonary veins isolation has also be shown to be superior, compared with AV node ablation and bi-ventricular pacing<sup>33</sup>.

### ***Rate control***

A lenient rate-control strategy (resting HR <110/min) has been compared with a strict rate-control one (resting HR <80/min and HR during moderate exercise <110/min) in a randomized controlled trial including 614 patients with permanent AF<sup>34</sup>. No differences in every outcome as well as in quality of life and LV remodeling was found between the two strategies and similar results were observed in a post-hoc analysis of the patients with concomitant HF<sup>34,35</sup>. However, these results do not mean absence of HR control in the lenient group. These patients had a baseline resting HR of 96+14/min and were treated with beta-blockers, non-dihydropyridine calcium antagonists and/or digoxin, alone or combined, in more than 85% of the cases. These data are consistent with a recent meta-analysis showing that tachycardia is predictive of poorer outcomes only in patients in sinus rhythm but not in those with AF<sup>36</sup>.

With respect of the drugs used for HR control, beta-blockers have been often considered as first choice, if tolerated, with a possible combination with digoxin and/or amiodarone. A recent meta-analysis has confirmed a beneficial effect on mortality of beta-blockers in the HF patients in sinus rhythm but not in those with AF<sup>37</sup>. When medical treatment is insufficient, AV node ablation with biventricular pacing is indicated<sup>2,38</sup>.

### ***Other supraventricular arrhythmias***

HR control is more difficult in the patients with atrial flutter or persistent supraventricular tachycardia and cardioversion is therefore needed. Patients with chronic atrial flutter have been shown to develop AIC, which improves after radiofrequency ablation<sup>39</sup>. Similar results were found in patients with supraventricular tachycardia or focal atrial tachycardia<sup>40</sup>.

### ***Ventricular arrhythmias***

Ventricular arrhythmias that can cause AIC include ventricular tachycardia and frequent, monomorphic, PVCs. They can cause AIC in a structurally normal heart or exacerbate HF in patients with preexistent heart disease<sup>5</sup>. In a study of 249 patients with idiopathic repetitive monomorphic PVCs and/or VT, 6.8 % had AIC, and 29% of these were asymptomatic<sup>13</sup>. All patients had an improvement in LVEF following treatment with either antiarrhythmics or radiofrequency ablation. The mechanism of PVCs mediated AIC may include

LV dyssynchrony, especially with a left bundle branch block PVC morphology, abnormal  $\text{Ca}^{2+}$  handling and abnormal LV filling. The daily burden of VPCs seems important, with a minimal threshold of 10.000 VPCs/day to cause AIC and an improvement in cardiac function when VPCs are reduced to <5.000 VPCs/day<sup>5</sup>. Therapy for PVC mediated AIC should be targeted at the suppression of the PVCs and may include anti-arrhythmics and catheter ablation. Beta-blockers and non-dihydropyridine calcium antagonists are often used as first-choice, as better tolerated. Other antiarrhythmics, such as sotalol and, above all, amiodarone, are more effective. Catheter ablation has emerged as a main treatment option and has been associated with an improvement in LV dimensions and EF<sup>2,5</sup>.

## Conclusions

AIC is under-diagnosed in many patients with HF. However, the diagnosis of AIC can be done only retrospectively, after the exclusion of other causes of HF, and an improvement in symptoms and cardiac function is shown after arrhythmia control. Treatment of the arrhythmia is therefore, by definition, associated with a better clinical course in patients with AIC. Few data, however, exist regarding how to treat such arrhythmias. For instance, in the case of AF, there is no evidence of benefits of a strategy of rhythm control, compared with a simpler strategy of rate control. Better results may be obtained with catheter ablation versus medical treatment. Moreover, in the case of rate control, a lenient strategy, aimed at a resting HR <100/min has achieved similar results, compared with a more aggressive one.

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