# Chapter 6
# Atrial Fibrillation and Heart Failure: Rate Versus Rhythm Control

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**Abstract** Atrial fibrillation and heart failure are commonly coexisting conditions with important pathophysiologic interactions impacting patient management. Treatment of atrial fibrillation with impaired ventricular function is focused towards preventing adverse hemodynamic effects that may result in more symptoms and decreased exercise tolerance. While rate control using medications or atrioventricular nodal ablation combined with pacing is the primary emphasis of management, rhythm control using pharmacologic or pulmonary vein isolation remains a feasible alternative strategy for some patients. The prevalence, mechanisms, and management strategies of atrial fibrillation and heart failure are reviewed in this chapter.

## 1 Introduction

Atrial fibrillation (AF) and heart failure (HF), two increasingly common and coexisting conditions encountered in the aging population, interact in ways that are distinct from the general population of AF patients without heart failure. In AF, the primary treatment goals focus on control of symptoms and reducing risk of stroke. Additionally, in the patient with AF and impaired ventricular function, treatment is focused towards preventing adverse hemodynamic effects that may result in more symptoms and decreased exercise tolerance.

Patients with heart failure have a higher risk of developing AF compared to the normal population. The prevalence of AF increases with worsening New York Heart

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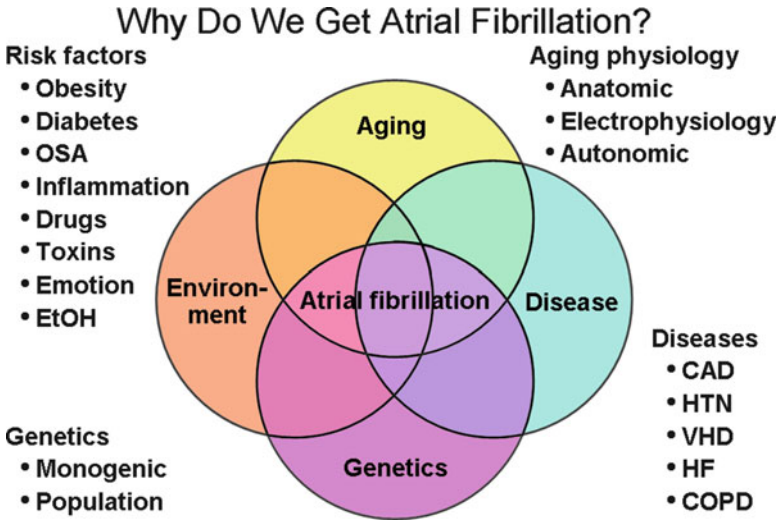


**Fig. 6.1** Atrial fibrillation is a multifactorial condition resulting from an interaction between cardiovascular disease effects, aging, genetics, and environmental factors. *CAD* coronary artery disease, *COPD* chronic obstructive pulmonary disease, *EtOH* alcohol use, *HF* heart failure, *HTN* hypertension, *OSA* obstructive sleep apnea, *VHD* valvular heart disease

Association (NYHA) functional class [1]. Additionally, patients with abnormal diastolic function but no clinical heart failure diagnosis also have an increased risk of developing AF [2].

Atrial fibrillation is a disease of the elderly, with 3 out of 4 AF patients between the ages of 65 and 85 years. Interplay between advancing age, comorbidities, and environmental and genetic factors contributes to the development of AF (Fig. 6.1). The prevalence of AF is currently 1–2 %, and is expected to increase with the aging population [3, 4]. Comorbid medical conditions associated with AF including hypertension (HTN), heart failure, valvular heart disease (VHD), cardiomyopathies, coronary artery disease (CAD), obesity, diabetes mellitus, chronic obstructive pulmonary disease (COPD), sleep apnea, and chronic kidney disease are more frequent in the elderly, play a role in propagating AF, and increase morbidity and mortality [5]. Hospitalizations for AF in the United States have increased dramatically (two to threefold) in the last 15 years [6]. The prevalence of heart failure also increases with age, with a lifetime risk of developing heart failure in men and women aged 40 years of 1 in 5 [7].

This chapter reviews the current understanding of the pathophysiology of AF in patients with heart failure, providing an in-depth discussion of evidence-based therapies for rhythm versus rate control therapy. Additionally, this chapter will discuss the rationale for pulmonary vein isolation (PVI) versus atrioventricular (AV) nodal ablation and pacing therapies in patients with AF and heart failure. Evidence for benefit of cardiac resynchronization therapy (CRT) in the setting of AF and heart failure will be highlighted.

## 2 Pathophysiology of Atrial Fibrillation and Heart Failure

### *2.1 Atrial Fibrillation as a Cause of Heart Failure*

#### 2.1.1 Mechanisms

In experimental animal models, it has been observed that chronic tachycardia can result in left ventricular (LV) dilatation with or without systolic dysfunction [8]. Persistent tachycardia depletes cellular high-energy stores in dogs such as creatine, phosphocreatine, and adenosine triphosphate [9]. These changes manifest in a reduced percentage of myocytes and reduced shortening velocity despite a higher LV mass [10]. The depletion of energy stores may be mediated by changes in cellular metabolism with mitochrondrial injury, increased activity of oxidative enzymes, and ischemia [11, 12]. In humans this now well-established entity of reversible congestive heart failure (CHF) in association with chronic tachycardia has been termed tachycardia-mediated cardiomyopathy [13–15].

Atrial fibrillation can also impair myocardial function by its irregular rhythm that produces variable durations of important components of the cardiac cycle, which can impair cardiac output. Furthermore, loss of atrial systole has a negative impact on ventricular filling and cardiac output [16].

The fall in cardiac output associated with AF often results in activation of neurohumoral vasoconstrictors including angiotensin II and norepinephrine, which may further impair ventricular function [17, 18]. Increased sympathetic nerve activity associated with AF is an effect that is partly mediated by the irregular ventricular response [19].

### *2.2 Heart Failure as a Cause of Atrial Fibrillation*

#### 2.2.1 Neurohumoral Activation and Mechanoelectrical Feedback

In CHF, neurohumoral activation of substances including angiotensin II and norepinephrine may promote atrial fibrosis [20, 21] with resultant changes in conduction properties that may predispose to AF. Acute atrial wall stretch is associated with increased dispersion of refractoriness and alterations in anisotropic and conduction properties facilitating AF [22]. Elevated filling pressures that occur in ventricular dysfunction lead to left atrial dilatation, which may stimulate stretch-activated channels and increase vulnerability to AF. Blockade of stretch-activated channels reduces the propensity for AF despite elevated atrial pressure and/or volume [23]. Additionally, left atrial enlargement may facilitate the stability and persistence of atrial fibrillation [24].

**Key Points**

- Atrial fibrillation can cause heart failure via tachycardia-mediated cardiomyopathy, impairment of cardiac output due to irregular cycle length and loss of atrial systole, and increased neurohumoral activation.
- Heart failure contributes to AF by neurohumoral and hemodynamic effects on atrial tissue including fibrosis, acute wall stretch, and chamber dilatation.

## 3 Prognosis of Atrial Fibrillation and Heart Failure

Several studies have suggested the development of AF is associated with a worse prognosis in patients with preexisting left ventricular (LV) dysfunction. In the Studies of Left Ventricular Dysfunction (SOLVD) prevention and treatment trial [25], AF at baseline was an independent predictor of mortality and morbidity, primarily related to heart failure, death, or rehospitalization for heart failure. In a substudy of the Danish Investigators of Arrhythmia and Mortality ON Dofetilide (DIAMOND) trial [26] of patients with an ejection fraction of 35 % or less, maintenance of sinus rhythm at 1 year was strongly and independently associated with survival, either with placebo or dofetilide. Further evidence that AF causes hemodynamic deterioration in patients with underlying LV dysfunction was provided by an observational study of 344 patients with compensated heart failure who were followed for 19 months [27]. The development of AF in 8 % of these patients was associated with worsening of NYHA functional class, an increase in left atrial size, an increase in both mitral and tricuspid regurgitation, and a reduction in cardiac index and peak oxygen consumption.

## 4 Current Management

Historically, rate control was considered a "fallback" therapy for AF after failed rhythm control. However, in recent years the practice has shifted from rhythm control to rate control, with rate control being a very feasible alternative therapy for management of AF.

### *4.1 Rate Control Strategy*

The concept of rate control for AF centers on the idea that the primary mechanism for symptoms in AF is tachycardia and the resultant shortening of the diastolic filling period. In addition to symptomatic improvement, many patients with LV dysfunction and AF experience an improvement in ejection fraction following control

of the ventricular rate [28, 29], likely reflecting an improvement in tachycardia-mediated ventricular dysfunction.

### 4.1.1 Medications

Beta-blockers are the preferred agent for rate control in atrial fibrillation, primarily due to their established beneficial effects in heart failure. When a second agent is required, digoxin is often a good choice, with the consideration that patients with impaired renal dysfunction are at higher risk for digoxin toxicity and require closer monitoring. Heart rate should be evaluated both at rest and with activity to determine if control is adequate. In patients with decompensated heart failure and rapid AF, increasing beta-blocker doses is contraindicated and digoxin can be used in this setting. When beta-blockers and digoxin are ineffective, amiodarone can be used alone or in combination with other rate-slowing agents to achieve rate control. Dronedarone slows the heart rate by 10 bpm [30] and should be avoided in any patients with NYHA class III or IV symptoms of heart failure due to its association with increased mortality [31]. Non-dihydropyridine calcium channel blockers carry a risk of exacerbating CHF and thus are generally avoided for this population.

**Key Points**

- Effective rate control medications for patients with AF and heart failure include beta-blockers, digoxin, and amiodarone.
- Rate control drugs to avoid in AF and symptomatic heart failure include dronedarone and calcium channel blockers.

### 4.1.2 Trials of Rate Control

Potential benefit of rate control in patients with heart failure was observed in a retrospective analysis of the US Carvedilol Congestive Heart Failure trial where 136 of 1,094 patients with heart failure due to systolic dysfunction had AF [28]. In this study, patients treated with carvedilol had a significant increase in the LV ejection fraction (from 23 to 33 % compared with 24 to 27 % with placebo), demonstrating a beneficial effect of carvedilol in this setting. There was also a trend towards a reduction in the primary endpoint of death or CHF hospitalization ($p = 0.06$). An important caveat is that the study did not prove that the benefit seen was due solely to rate control as opposed to the other neurohumoral effects of beta blockade.

The AF-CHF trial randomized patients with heart failure and paroxysmal AF to medical therapy with either rhythm (amiodarone, sotalol, or dofetilide) or rate control (beta-blockers) [32]. After a 3-year follow-up period, there was no difference in cardiovascular mortality between the two groups (Fig. 6.2). This study supports the concept that a rate control strategy is a more reasonable initial approach for the majority of patients with AF and heart failure due to the increased cost, complexity

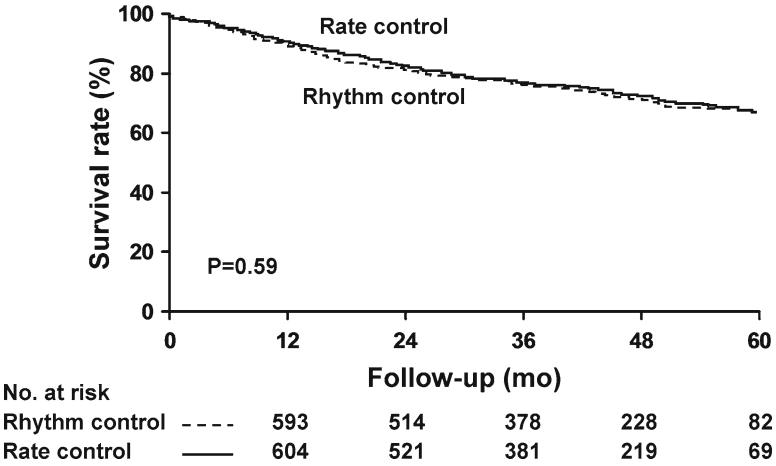


**Fig. 6.2** Kaplan Meier estimates for death from cardiovascular causes for patients with atrial fibrillation and heart failure treated with either rate or rhythm control [32]. Permission obtained from The Massachusetts Medical Society

of medical regimen, and potential adverse affects associated with antiarrhythmic therapy.

The RACE II trial compared strict (resting heart rate <80 bpm and heart rate during moderate exercise <110 bpm) versus lenient (resting heart rate <110 bpm) rate control in the AF population [33]. In this study 10 % of patients also had a history of heart failure, and there was no significant difference in the outcome of death from cardiovascular causes, hospitalization for heart failure, stroke, embolism, bleeding, and life-threatening arrhythmic events between the two groups. Based on this trial and other data in the literature (Table 6.1), a goal of average resting heart rate <110 bpm may be a reasonable starting point. However, more data on degree of rate control are needed in the heart failure population.

**Key Points**

- Rate control of AF in patients with heart failure is associated with improved clinical outcomes.
- Available evidence suggests that rate control has similar benefits as rhythm control in AF and heart failure.

### 4.1.3 Effect of Pacemaker Therapy on Risk of Atrial Fibrillation and Heart Failure

The choice of dual chamber pacing versus single chamber pacing in patients who require a permanent pacemaker may have an impact on their subsequent risk of AF and heart failure. In 2002, the MOST study randomized 2,010 patients with sinus node dysfunction requiring a pacemaker to either dual chamber or single chamber

**Table 6.1** Trials of rate control in atrial fibrillation and heart failure

| Author/year | Population | Design | Primary endpoint | Results |
|---|---|---|---|---|
| Joglar et al. [28] | Symptomatic CHF, EF <35 % with AF (136 patients) | Retrospective analysis of a randomized trial of carvedilol versus placebo | Death or CHF hospitalization | Trend towards reduction in primary endpoint (7 % versus 19 %, $p=0.06$) and improvement in EF (24–33 %, $p=0.001$) w/ carvedilol versus placebo |
| Roy et al. [32] (AF-CHF) | Symptomatic CHF, EF <35 % with AF (1,376 patients) | Randomized multicenter trial of rate versus rhythm control | Cardiovascular death | No difference in primary endpoint at 3 years (25 % versus 27 %, $p=0.59$) |
| Van Gelder et al. [33] (RACE II) | Persistant AF (10 % of patients had prior hospitalization for CHF) | Randomized multicenter trial of lenient versus strict rate control | Composite of death from cardiovas-cular causes, hospitalization for CHF, and stroke, systemic embolism, bleeding, and life-threatening arrhythmic events | No difference in primary endpoint at 3 years (12.9 % versus 14.9 %, non-inferiority $p<0.001$) |

*AF* atrial fibrillation, *CHF* congestive heart failure, *EF* ejection fraction, *RACE II* rate control efficacy in permanent atrial fibrillation trial

ventricular pacing to determine if there was a difference in the primary endpoint of death or nonfatal stroke [34]. The median age of this population was 74 and comorbidities included prior myocardial infarction in 26 %, prior heart failure in 20 %, diabetes in 22 %, and history of AF in 46 %. There was no difference in the primary endpoint ($p = 0.48$), however a lower incidence of AF and heart failure was observed in the dual chamber pacing group, at almost 3 years of follow-up suggesting a protective effect of dual chamber pacing in this population. This data reinforces that dual chamber pacing is preferred for patients requiring a permanent pacemaker, in order to maintain AV synchrony and reduce the long-term risk of AF and heart failure.

### 4.1.4 AV Nodal Ablation with Pacing

AV nodal ablation and pacing provides an attractive means to control AF, particularly in patients with drug-refractory AF or in those who cannot tolerate medications due to intolerances or impaired ventricular function. AV nodal ablation is highly effective (>95 % procedural success), but is also a more invasive option that leaves patients pacemaker-dependent. Emerging evidence in the population undergoing AV nodal ablation for AF supports the role of CRT due to the beneficial effects associated with preserved ventricular synchrony (Table 6.2). PVI, although a preferred rhythm-control option for drug-refractory AF patients with normal LV function, has been infrequently used in heart failure population due to a higher prevalence of comorbidities and structural features that are associated with reduced procedural success.

In a prospective, small randomized trial of 81 patients with class II or III heart failure and ejection fraction <40 % who had symptomatic, drug-refractory AF, PVI for rhythm control was compared with AV nodal ablation and biventricular (BiV) pacing for rate control [35]. At 6 months, PVI was associated with statistically significant improvements in left ventricular ejection fraction (35 % versus 28 %), 6-min walk distance (340 versus 297 m), and score on the Minnesota Living with Heart Failure questionnaire. The improvements in ejection fraction and functional capacity were greater for those with nonparoxysmal compared to paroxysmal AF. In addition, approximately 30 % of patients treated with AV node ablation and biventricular pacing had progressive AF (e.g., paroxysmal to persistent AF); such progression was not seen in patients treated with PVI. Although encouraging, this study only provided short-term data, and the long-term efficacy of PVI in the AF and heart failure population is unknown.

The dual-chamber and VVI implantable defibrillator (DAVID) trial randomized over 5,000 patients with ejection fraction <40 % and indication for an implantable cardioverter defibrillator to either ventricular back-up pacing at 40/min or dual-chamber rate-responsive pacing at 70/min [36]. Patients in the dual chamber pacing group had an increased combined endpoint of mortality and hospitalization for CHF. The increased heart failure and mortality was believed to be due to the maladaptive features of RV stimulation, where ventricular electrical activation proceeds

**Table 6.2** Trials of CRT in chronic AF

| Authors | Year | Number studied | Population | Intervention | Outcome | Results |
|---|---|---|---|---|---|---|
| Leclerq et al. | 2002 | 59 | NYHA class III systolic heart failure undergoing pacemaker implant | CRT versus RV pacing | 6 min walk distance and oxygen uptake | Favors CRT (mean walk distance increased 9.3 % ($p=0.05$) and peak $VO_2$ increased by 13 % ($p=0.04$) over RV pacing) |
| Linde et al. | 2002 | 33 | NYHA class III heart failure and pacemaker dependent from either acquired AV block or induced AV nodal ablation | CRT versus RV pacing | 6 min walk distance and NYHA class | Favors CRT (mean walk distance improved by 17% ($p=0.004$) and NYHA class improved by 27 % over RV pacing ($p=0.0001$)) |
| Brignole et al. | 2005 | 56 | Age 70 ± 8 years with symptomatic persistent AF and either uncontrolled ventricular rate or heart failure | CRT versus RV pacing | Quality of life questionnaires, NYHA class, 6 min walk distance, and ejection fraction | Favors CRT (NYHA class improved by 11 % pacing, 6 min walk distance improved by 4 m, and EF improved by 5 % compared with RV ($p<0.05$ for all)) |
| Doshi et al. | 2005 | 184 | Age 69 ± 10 years undergoing AVN ablation | CRT versus RV pacing | 6 min walk distance and ejection fraction | Favors CRT (6 min walk 31 % improvement with CRT versus 24 % improvement with RV pacing over baseline, $p=0.04$) EF 46 ± 13 % versus 41 ± 13 % ($p=0.03$) |

*AF* atrial fibrillation, *CRT* cardiac resynchronization therapy, *EF* ejection fraction, *NYHA* New York Heart Association, *RV* right ventricular, $VO_2$ oxygen consumption

from the right ventricular apex instead of through the existing conduction system, leading to ventricular desynchronization. Although this mechanism was not proven to be the cause of worse outcome, it supported the concept that patients with heart failure requiring frequent ventricular pacing would benefit from CRT.

Observational studies and small randomized trials support the value of CRT for improving symptoms and left ventricular function in patients with poorly controlled AF who have reduced LV systolic function or heart failure [37, 38]. In a small randomized control trial of patients with symptomatic, medically refractory, chronic, rapid AF assigned to AV nodal ablation with either RV pacing or CRT, the group with CRT showed greater improvement in exercise tolerance and greater preservation of ejection fraction [39]. A meta-analysis of three randomized CRT AF trials [37, 40–42] showed a trend towards improved survival among patients randomized to CRT but the difference in survival among patients randomized to CRT versus RV pacing was not statistically significant [43].

A recent observational cohort study of patients with AF and heart failure who received CRT-D showed that AV nodal ablation for definitive biventricular pacing provided a greater improvement in NYHA class and survival benefit compared with drug therapy for rate control [44]. In 154 patients with a median follow-up of 274 days, the median (Q1, Q3) percentage of biventricular pacing after CRT was 99.0 % (95–100 %) in the AV nodal ablation group compared to 96.0 % (85.5–99.0 %) in the drug-treated group ($p=0.05$). After CRT, both groups had significant improvements in NYHA class, LV ejection fraction, and LV end diastolic dimension. Improvement in NYHA class was significantly greater in the AV nodal ablation group compared to the drug-treated group ($0.7 \pm 0.8$ versus $0.4 \pm 0.8$, $p=0.04$), while improvement in echocardiographic parameters was not significantly different between the two groups.

**Key Points**

- Dual chamber pacing helps maintain AV synchrony and reduces the long-term risks of AF and heart failure in patients requiring a permanent pacemaker.
- Radiofrequency ablation of the AV node combined with permanent right ventricular endocardial pacing is a highly effective treatment for controlling the ventricular response of AF.
- The elderly population is particularly suited to AV nodal ablation and permanent pacing for treatment of AF due to higher frequency of comorbidities, risks of medication intolerance, and the relative safety and simplicity of the procedure.
- CRT is beneficial for patients with AF and reduced left ventricular systolic function who require frequent pacing.

## *4.2 Rhythm Control Strategy*

Rhythm control may be a reasonable approach in patients with heart failure who are hemodynamically unstable or who are persistently symptomatic despite adequate rate control [45]. Several factors impact the likelihood of successful restoration and

long-term maintenance of sinus rhythm, including how long a patient has been in persistent AF, their age, the presence of associated structural heart disease, and left atrial size. Antiarrhythmic drug therapy and radiofrequency catheter ablation are the two primary therapies for rhythm control.

Direct current electrical cardioversion is a useful therapy for patients with new onset AF alone or in combination with antiarrhythmic therapy, and can also be helpful for patients with symptoms that are not clearly attributable to AF. In such patients, when symptoms and functional status improve after cardioversion to sinus rhythm, AF is probably an important factor. In this way cardioversion is helpful in the diagnostic approach to symptoms. Cardioversion is also useful in the management of hemodynamically unstable patients with AF and LV dysfunction. In this group, cardioversion can rapidly improve hemodynamics via restoration of normal cardiac cycle, atrial systole, and decreasing heart rate thus improving diastolic filling time. Cardioversion is more likely to result in sustained maintenance of sinus rhythm in this population when combined with an antiarrhythmic drug.

### 4.2.1 Antiarrhythmic Therapy

Amiodarone and dofetilide are the first-line therapies for maintenance of sinus rhythm in patients with AF and heart failure recommended by the ACC/AHA/HRS guidelines [46]. Amiodarone has the advantage of being a potassium channel blocker with both beta-blocking and calcium channel-blocking effects. As a result, it has a negative inotropic effect and tends to control the ventricular rate when in atrial fibrillation. Furthermore, amiodarone has been shown to have a low incidence of QT prolongation and less pro-arrhythmia when used in low doses (400 mg per day or less) in patients with heart failure [47]. Compared with dofetilide, additional advantages of amiodarone include its once daily dosing, reduced cost, and ability to start therapy as an outpatient.

### 4.2.2 Pulmonary Vein Isolation

Although not commonly used as a treatment strategy in the AF population with heart failure, catheter ablation of AF can be successful in patients with concomitant heart failure. In a small observational study of 58 patients undergoing catheter ablation for AF with NYHA class II or greater symptoms and LV ejection fraction <45 %, symptoms, LV function, and exercise capacity were all improved at 12 months [48]. In another observational study 94 patients with impaired LV systolic function (mean ejection fraction 36 %) underwent PVI [49]. After approximately 1 year of follow-up 73 % of the study patients remained AF-free compared to 87 % in a control group of patients with ejection fraction >50 % ($p<0.001$). In this study, there was a nonsignificant trend towards improved ejection fraction following ablation in the study group. These data provide some evidence that PVI can improve

clinical outcomes in heart failure patients up to 1 year following ablation. However, the long-term durability of the procedure in this population remains unknown.

**Key Points**

- Rhythm control in AF and heart failure is useful in patients who are hemodynamically unstable or patients with persistent symptoms from AF despite adequate rate control.
- Electrical cardioversion (usually combined with antiarrhythmic medication) is useful for hemodynamically unstable patients and in patients with symptoms that are not clearly attributable to AF.
- First-line antiarrhythmic medications are amiodarone and dofetilide for AF and heart failure.
- Catheter ablation of AF can be successful in patients with heart failure, but long-term durability remains unknown.

## 5 Future Trends

The CHALLENGE pilot study is currently recruiting patients to test the hypothesis that AV nodal ablation compared to drug therapy improves outcomes in patients with AF and symptomatic heart failure undergoing CRT. This study is based on the idea that intermittent AV nodal concealed penetrance and ventricular conduction during AF can interrupt CRT pacing and ventricular synchrony, especially in situations of increased myocardial demand (i.e., during exercise). Occurrence of fusion or pseudo-fusion beats may overestimate the amount of "effective" CRT pacing. As a result, optimal clinical benefits may not be achieved even when the device records greater than 80–85 % pacing. It is anticipated that the study will offer valuable insight into whether the ability of AV nodal ablation to achieve 100 % CRT pacing provides a superior clinical effect.

## 6 Conclusions

Atrial fibrillation and heart failure are two increasingly common conditions in the developed world. In patients with underlying structural heart disease and LV dysfunction, AF can precipitate hemodynamic deterioration and adverse clinical events. AF is also a cause of reversible LV dysfunction in patients without structural heart disease (AF-induced cardiomyopathy) and should be considered when patients present with newly recognized heart failure or AF. When rate control of AF is achieved by either medications or AV nodal ablation with pacing, many hemodynamic consequences of tachycardia may be abated, and ventricular function can improve. In patients with AF and heart failure requiring pacing, increasing data supports the use of CRT to optimize ventricular mechanical synchrony. Ongoing

studies will help determine whether AV nodal ablation improves response to CRT in this population. Rhythm control with drug therapy or PVI remains an option, but is generally less successful than rate control.

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