Management of atrial fibrillation in the setting of heart failure

H. J. G. M. Crijns, M. P. Van Den Berg, I. C. Van Gelder and D. J. Van Veldhuisen

Department of Cardiology, Thoraxcenter, University Hospital Groningen, Groningen, The Netherlands

Heart failure is often complicated by atrial fibrillation. Once atrial fibrillation has started it further enhances heart failure due to uncontrolled rate with shortened filling time and provocation of tachycardiomyopathy. Absent atrial kick and irregularity of the ventricular rhythm also contribute. Considering these mechanisms, restoration of sinus rhythm is most beneficial but is associated with frequent recurrences. Before cardioversion heart failure must be treated. ACE inhibition, initiated before cardioversion, may enhance maintenance of sinus rhythm by reducing neurohumoral activation. As a consequence, arrhythmogenic factors diminish and ventricular function may improve. /-blockade and amiodarone may have similar effects. If cardioversion fails, adequate rate control is mandatory to prevent progressive ventricular dysfunction. Digitalis is the treatment of first choice, but when the heart rate remains uncontrolled low-dose /-blockade should be given.

If the ventricular rate remains uncontrolled despite drugs, atrioventricular node ablation with implantation of a pacemaker may be considered. Not only patients with idiopathic heart failure and atrial fibrillation, but also those with significant underlying heart disease may benefit from this intervention. In atrial fibrillation patients undergoing cardiac surgery for heart failure due to valvular disease, additional arrhythmia surgery may be contemplated.

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Importance of heart failure as a risk for atrial fibrillation

Heart failure is the most frequent precursor of atrial fibrillation. The relative risk for developing atrial fibrillation in the Framingham study was 4.5 and 5.9 in men and women, respectively. Of all men developing atrial fibrillation during 38 years of follow-up, 20.6% had congestive heart failure at inclusion versus only 3.2% of those without atrial fibrillation. These figures were 26.0% and 2.9% in women, respectively. In addition, the largest population-attributable risk (i.e. the percentage of preventable atrial fibrillation if a causal risk factor could be eliminated from the population) was found for hypertension (14% for both sexes) followed by congestive heart failure: 10 and 13% of all atrial fibrillation cases in men and women, respectively.

In the Reykjavik study, 25 subjects with chronic atrial fibrillation (found in a population of 9062, atrial fibrillation prevalence 0.28%) were followed for 14 years. Prevalence of congestive heart failure was 12% compared with 0% in a matched control group of 50 subjects in sinus rhythm. At the end of follow-up, 36% of chronic atrial fibrillation individuals had developed heart failure versus only 2.1% of controls. Therefore, atrial fibrillation may also precede heart failure, a finding not reported from the Framingham study.

To our knowledge there are no data concerning the incidence of atrial fibrillation during long-term follow-up in patients referred for management of heart failure. Usually these data are not reported separately or the atrial fibrillation definition is unclear. By contrast, the prevalence of atrial fibrillation in patients referred for management of heart failure is well known: 15–20% are in atrial fibrillation at inclusion. The prevalence of symptomatic heart failure — as evidenced by NYHA class III or IV for exercise tolerance — in larger hospital populations referred for cardioversion of chronic atrial fibrillation, is even larger and varies between 27% and 48%. From the latter studies it appears that only a minority of patients with chronic atrial fibrillation will actually develop heart failure as a consequence of the arrhythmia per se (tachycardiomyopathy). Van Gelder et al. showed that of patients with chronic atrial fibrillation and minimal or absent underlying heart disease, no one developed overt heart failure. Patients with overt heart failure during follow-up were those who also had left ventricular dysfunction at baseline.

Correspondence: Harry J. G. M. Crijns, MD, Department of Cardiology, Thoraxcenter, University Hospital Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands.

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The impact of atrial fibrillation on mortality in patients treated initially for heart failure is uncertain. Carson et al.\(^3\) reporting for the VHeFT-I and -II could not find a prognostic impact whereas Middlekauff et al.\(^6\) showed that atrial fibrillation may affect prognosis especially in patients with lower filling pressure (pulmonary wedge pressure <15 mmHg). The discrepancy between these two large studies may relate to differences in baseline severity of heart failure (average left ventricular ejection fraction 30 versus 19%, NYHA II–III versus mainly NYHA IV, respectively), with relatively more patients with established atrial fibrillation (49 of 75 patients) in the study by Middlekauff et al. In addition, antiarrhythmic drug treatment and anticoagulation were not controlled. The percentage of patients using antiarrhythmics in VHeFT was significantly lower. Possibly proarrhythmia, especially with class I drugs may have worsened prognosis in atrial fibrillation patients in the study of Middlekauff et al. Considering the above findings it may be speculated that atrial fibrillation has an impact on prognosis only late in the course of the disease, i.e. when heart failure has progressed to NYHA classes III and IV.

**Pathophysiological mechanisms and their relevance for treatment**

The pathophysiology of heart failure is characterized by haemodynamic and neurohumoral derangements. Once heart failure has emerged, atrial fibrillation can be triggered through an increase of atrial pressure and volume. These changes may cause stretch-related arrhythmias by inducing abnormal automaticity and triggered activity. Atrial stretch is also associated with slowing of conduction, and shortening and increased dispersion of refractoriness which may facilitate re-entrant arrhythmias.\(^5\)-\(^9\) Unloading of the heart using standard heart failure treatment is therefore important to prevent atrial fibrillation. Additional atrial enlargement may occur due to longstanding arrhythmia per se, which has been found even in patients with congestive heart failure.\(^10\)

The neurohumoral disturbance is further contributed to by activation of the autonomic nervous and the renin-angiotensin systems, which, beside aggravating heart failure, promote the above arrhythmogenic mechanisms. Neurohumoral activation may also induce hypertrophy and, at later stages, fibrosis in the atria, thereby further facilitating arrhythmias.\(^5\)-\(^9\). These changes may be blocked by ACE inhibition or \(\beta\)-blockade.

Once atrial fibrillation has occurred, atrial tachycardiomyopathy (high metabolic demand, secondary regressive cellular changes) and further shortening of refractoriness will develop.\(^12\)-\(^13\). The latter changes presumably develop over the course of weeks and are the main reason why the arrhythmia may become resistant to cardioversion strategies. In addition, the fall in cardiac output associated with the onset of atrial fibrillation intensifies the neurohumoral imbalance thereby worsening both heart failure and atrial fibrillation (Fig. 1). To prevent atrial fibrillation from becoming permanent, early restoration of sinus rhythm is advocated although this is difficult in the setting of the unfavourable haemodynamic and neurohumoral circumstances. A combined approach of haemodynamic unloading, neurohumoral modulation and electrical cardioversion possibly supported by amiodarone may help suppress atrial fibrillation.\(^14\)-\(^15\).

Compared with patients in sinus rhythm, adrenergic activation — initially induced by heart failure — has an additional effect in atrial fibrillation, precipitating an important vicious circle (Fig. 1). By facilitating atiuroventricular conduction (leading to an increased ventricular response), cardiac output is further reduced, in particular during exercise, leading to amplification of heart failure. This vicious circle makes up the basis of tachycardiomyopathy in atrial fibrillation patients and may occur even in 'lone' arrhythmia. Rigid rate control is mandatory but, paradoxically, physicians are reluctant to prescribe negative chronotropics such as verapamil, diltiazem or \(\beta\)-blockers (for their potential negative inotropic effects). Considering the above, \(\beta\)-blockade in addition to the neurohumoral modulator digoxin may give further benefit in this setting.
Effects of rhythm control in atrial fibrillation complicated by heart failure

Electrical cardioversion

Electrical cardioversion is the best option in terms of restoration of physiological rate control. After restoration of sinus rhythm, left ventricular systolic function may increase significantly during follow-up and discontinuation of negative inotropic drugs. Apart from these hemodynamic factors, the reversal of tachycardiomyopathy due to deactivation of the neurohumoral and renin-angiotensin system may also play a role.

Cardioversion should be performed after heart failure has been treated effectively. Pre-treatment with ACE inhibition, which also has neurohumoral effects, may be an effective approach. However, postponing cardioversion may lengthen the time in atrial fibrillation, thereby reducing the chance of restoring sinus rhythm.

Especially in atrial fibrillation complicated by heart failure, antiarrhythmic drugs have low efficacy for maintaining sinus rhythm and carry a substantial risk of adverse effects including proarrhythmia, conduction disturbances and aggravation of heart failure. Flaker et al. showed that class IA and IC drugs enhanced the sudden death rate more than three-fold compared with patients not using these agents. Of the class III drugs, sotalol may induce torsade de pointes especially in patients with heart failure. By contrast, low-dose amiodarone has been shown to be effective in atrial fibrillation and heart failure and the number of side effects may be limited. Amiodarone does not adversely affect mortality in patients with heart failure. Apart from suppression of atrial fibrillation, amiodarone may achieve ventricular rate control in permanent atrial fibrillation. The experience with prophylactic use of amiodarone after cardioversion of atrial fibrillation in patients with heart failure is, however, limited. Gosselink et al. reported a small subgroup of 14 patients in which amiodarone was effective in advanced heart failure (28%) with a 93% maintenance of sinus rhythm after an average of 3 years. Similarly, Middlekauff et al. reported beneficial effects of amiodarone in 25 patients with advanced heart failure (NYHA class III-IV) and drug-refractory atrial fibrillation. In 84% of patients, sinus rhythm was restored pharmacologically or after direct current cardioversion and at one year 87% of patients were still in sinus rhythm. Chun et al. studied a mixed group of atrial fibrillation patients with and without heart failure. They demonstrated that as the long-term antiarrhythmic efficacy and safety of amiodarone did not depend on baseline ejection fraction, amiodarone was appropriate for patients with left ventricular dysfunction.

Pharmacological rate control

Pharmacological rate control is usually achieved with digoxin, calcium channel blockers or β-blockers. Digoxin may control heart rate at rest but is ineffective in controlling exercise heart rate. If necessary verapamil or β-blockers can be added. Although the addition of verapamil will result in a reduction of the ventricular rate, sympathetic activation due to concomitant vasodilation may hamper improvement of left ventricular function. β-blockers have a similar effect on ventricular rate, although as they do not induce neurohumoral activation, they may help to improve cardiac function. To prevent worsening of heart failure, careful dose titration is indicated.

Atrioventricular node ablation and permanent pacemaker implantation

The role of catheter ablation and pacemaker implantation in the treatment of atrial fibrillation complicated by heart failure has not been defined yet. Several uncontrolled studies, however, have shown that after this procedure ventricular function may improve significantly.

Identification of patients who will benefit from cardioversion or atrioventricular node ablation

Electrical cardioversion of atrial fibrillation in patients with heart failure is associated with frequent arrhythmia recurrence. Many attempts may be necessary to suppress the arrhythmia. Atrioventricular node ablation and insertion of a pacemaker is not yet generally accepted and is considered expensive. Therefore it is important to predict which patient will show hemodynamic benefit from serial electrical cardioversions or atrioventricular node ablation. As yet there is no answer to this question since all studies reporting beneficial effects of cardioversion or atrioventricular node ablation were uncontrolled (Table 1). The relative timing of atrial fibrillation and heart failure as well as the uncontrolled ventricular rate despite drug therapy must be relevant. One would expect significant clinical improvement if it could be proven that atrial fibrillation preceded the development of heart failure. In addition, in patients with an uncontrolled rate, reversal of tachycardiomyopathy might be anticipated after adequate rate control with cardioversion or atrioventricular node ablation. Table 1 shows the clinical characteristics of patients who had a significant increase of ejection fraction after such interventions. These data suggest that, in many patients, the resting heart rate may have been important in the development of left ventricular dysfunction. The studies by Kieny and Natale and co-workers showed that patients without a fast heart rate may also respond. However, these
Table 1  Clinical characteristics of atrial fibrillation patients with left ventricular dysfunction or congestive heart failure, showing haemodynamic benefit of cardioversion or atrioventricular node ablation

<table>
<thead>
<tr>
<th>First author</th>
<th>Mode of rhythm control</th>
<th>Age (years)</th>
<th>HR at rest (beats · min⁻¹)</th>
<th>Aetiology of AF and heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kieny</td>
<td>ECV</td>
<td>58</td>
<td>84</td>
<td>Idiopathic CMP</td>
</tr>
<tr>
<td>Grogan</td>
<td>ECV/RC</td>
<td>52</td>
<td>145 ± 17</td>
<td>Idiopathic CMP</td>
</tr>
<tr>
<td>Van Gelder</td>
<td>ECV</td>
<td>60</td>
<td>123 ± 28</td>
<td>Idiopathic AF</td>
</tr>
<tr>
<td>Heinz</td>
<td>HBA</td>
<td>64</td>
<td>&gt;120</td>
<td>Idiopathic AF</td>
</tr>
<tr>
<td>Rodriguez</td>
<td>HBA</td>
<td>60</td>
<td>112 ± 9</td>
<td>Idiopathic AF</td>
</tr>
<tr>
<td>Twidale</td>
<td>HBA</td>
<td>63</td>
<td>140 ± 25</td>
<td>CAD/valve/idiopathic CMP</td>
</tr>
<tr>
<td>Brignole</td>
<td>HBA</td>
<td>67</td>
<td>&gt;100</td>
<td>CAD/valve/idiopathic CMP</td>
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<tr>
<td>Edner</td>
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<td>68</td>
<td>—</td>
<td>CAD/valve/idiopathic CMP</td>
</tr>
<tr>
<td>Natale</td>
<td>HBA</td>
<td>66</td>
<td>60-100</td>
<td>—</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; CAD = coronary artery disease; CMP = cardiomyopathy; ECV = electrical cardioversion; HBA = His bundle ablation; HR = heart rate; RC = rate control with negative chronotropic drugs; valve = valvular heart disease.

All studies were uncontrolled.

studies did not mention heart rate during exercise. In patients with atrial fibrillation and heart failure, the chronotropic response during exercise is enhanced at low levels of exercise while the resting heart rate may be normal[14,31,32]. Presumably, comparable heart rates are achieved during normal daily activities resulting in relatively high average daytime ventricular rate. Future studies may indicate whether exercise heart rate is a useful parameter for selecting patients for cardioversion or atrioventricular node ablation.

Management of atrial fibrillation in the setting of heart failure: the arrhythmologist’s view

The first step in the treatment of atrial fibrillation in patients with heart failure is to deal with underlying conditions and reduce congestion with ACE inhibitors and diuretics (Fig. 2). In addition, oral anti-coagulation will reduce thromboembolic complications[33]. At the same time, rate control should be optimized. Paradoxically, heart failure patients are frequently not well treated in this respect despite the fact that rigid rate control is essential to prevent further worsening of left ventricular function. Optimal rate control includes reducing resting heart rate to <80–90 beats · min⁻¹[34] and preventing excessive rate responses (below 120 beats · min⁻¹) on minimal exercise[14,32]. Digitalis is the treatment of first choice, but when the heart rate remains uncontrolled, low-dose β-blockade rather than calcium channel blockers should be added. Sotalol must be avoided because of its proarrhythmic effects and lack of a significant advantage over conventional (low-dose) β-blockade.

In selected cases, restoration of sinus rhythm may be attempted. In patients with left ventricular dysfunction but without overt heart failure this may be done early in the course of treatment. Considering the high recurrence rate in patients with a history of overt heart failure, cardioversion should be considered only for younger patients with a relatively short arrhythmia duration who are nearly asymptomatic (NYHA class I-II)[35]. Additionally, atrial size may play a role in this decision. In patients with late recurrences and in whom the haemodynamic benefit of restored sinus rhythm has been proved, serial electrical cardioversions (resulting in e.g. one shock per year) may be an option. Such an approach can be supplemented by low-dose amiodarone. Amiodarone may be especially valuable for patients with a history of overt failure[22,23].

If the cardioversion strategy fails or is not an option, and heart rate remains uncontrolled despite drugs, atrioventricular node ablation with implantation of a pacemaker may be useful. Of note, not only patients with idiopathic heart failure and atrial fibrillation, but also those with significant pathology such as coronary artery or valvular heart disease may benefit from this
intervention (Table 1). In atrial fibrillation patients undergoing valvular cardiac surgery for heart failure, additional arrhythmia surgery may be contemplated.

References


