

Atrial Fibrillation and Heart Failure

PANOS E. VARDAS, HERCULES E. MAVRAKIS

Cardiology Department, Heraklion University Hospital, Crete, Greece

Key words:
**Atrial fibrillation,
heart failure,
prognosis.**

The incidence of atrial fibrillation in the general population ranges around the same level as that of heart failure and is about 1-2%. It is important to note that the incidence of both diseases increases significantly with age.¹⁻⁴

Atrial fibrillation and heart failure share common risk factors for their development and for this reason they often co-exist. Chronic heart failure appears in more than 50% of patients with atrial fibrillation, while the incidence of atrial fibrillation increases progressively with a worsening in the NYHA functional class of heart failure.⁵⁻⁸

In all, 15-20% of patients with heart failure are in atrial fibrillation on their first evaluation,⁹ while 27-48% of patients who undergo cardioversion of chronic atrial fibrillation show a symptomatology of NYHA class III-IV heart failure.¹⁰

In the Framingham study, the relative risk of developing atrial fibrillation in patients with heart failure was 4.5 and 5.9 for men and women, respectively. Out of the male population who had atrial fibrillation during a 38-year follow up, 20.6% had heart failure at the start of the study, compared with 3.2% for patients who were in sinus rhythm. The percentages for women were 26% and 2.9%, respectively.¹¹

It has been established that the most significant risk factors for the development of atrial fibrillation are hypertension and heart failure. The elimination of hypertension and heart failure from the

general population would reduce the incidence of atrial fibrillation by 14% and 10-13%, respectively.^{11,12} The onset of atrial fibrillation can cause acute heart failure or can exacerbate previously existing chronic heart failure.¹³ There is also evidence that atrial fibrillation is aetiologically involved in causing tachycardiomyopathy due to the rapid ventricular response, and cases have been reported where heart failure regressed after restoration of sinus rhythm or control of the ventricular response.^{14,15,24}

Mechanisms of atrial fibrillation development in patients with heart failure

Heart failure is characterised by haemodynamic changes that increase the pressure and the volume of the atria and lead to disturbances of atrial electrical properties favouring the development of atrial fibrillation. More specifically, the atrial myocardium develops abnormal automaticity and triggered activity and shows increased dispersion of refractoriness.¹⁶ In a recent study it was found that in patients with heart failure the changes in atrial electrophysiological properties that promote the appearance of atrial fibrillation consist of increases in conduction time, effective refractory period, P wave duration and corrected sinus node recovery time. At the same time a significant increase was found in both the number and the duration of double potentials associated with areas of low voltage or elec-

Address:

Panos E. Vardas

*Cardiology Department,
Heraklion University
Hospital
P.O.Box 1352
Heraklion, Crete,
Greece
e-mail:
cardio@med.uoc.gr*

trical silence. Also, in patients with heart failure it was easier to induce atrial fibrillation with single extrastimuli and the arrhythmia was more often sustained.¹⁷

The neurohormonal changes caused by heart failure, mainly the activation of the renin-angiotensin-aldosterone system and the increased sympathetic activity, exacerbate the above-mentioned mechanisms of arrhythmogenesis. In addition, the neurohormonal stimulation promotes hypertrophy and fibrosis of the atria, thus rendering them even more susceptible to the development of atrial fibrillation.¹⁸ These neurohormonal changes can be treated using angiotensin converting enzyme inhibitors¹⁸ and β -blockers. The appearance of atrial fibrillation and its persistence over a long period of time lead to tachycardiomyopathy, dilation of the atria and further shortening of the atrial refractory period. These latter changes comprise the main reason why atrial fibrillation is resistant to attempts at cardioversion.¹⁹⁻²¹

Furthermore, the haemodynamic deterioration caused by the onset of atrial fibrillation accentuates the neurohormonal stimulation and aggravates both the heart failure and the arrhythmia. Specifically, the increased sympathetic activity increases atrioventricular conduction and the ventricular response to atrial fibrillation, especially during physical exercise, leading to a reduction in cardiac output and a deterioration in the heart failure.

It is therefore clear that the treatment of atrial fibrillation in patients with heart failure requires improvement of the patient's haemodynamic condition, alteration of the neurohormonal changes and either early cardioversion of the arrhythmia or adequate pharmaceutical control of the heart rate.

Haemodynamic consequences of atrial fibrillation in heart failure

It has been claimed that the increased RR variability in atrial fibrillation causes a worsening of left ventricular function and haemodynamic condition, regardless of the effect of atrial fibrillation on the ventricular rate.²² Other mechanisms that contribute to a deterioration in the patient's haemodynamic state include the following:

- loss of atrioventricular synchrony;
- a reduction of filling pressure in both ventricles leading to a reduction in stroke volume;
- an increase in mean atrial diastolic pressure;
- a reduction in the ventricular isovolumic relaxation time.

Also, data from the SOLVD study²³ suggest that atrial fibrillation compromises left ventricular function, while as stated above, a rapid ventricular response may cause tachycardiomyopathy.²⁴

We must thus conclude that atrial fibrillation and heart failure make up a vicious circle, since heart failure promotes the occurrence of atrial fibrillation and atrial fibrillations exacerbates heart failure.

Effect of atrial fibrillation on the prognosis of patients with heart failure

Developments in the treatment of heart failure have led to an improvement in mortality⁶ and a reduction in the incidence of concomitant atrial fibrillation. Effective treatment of atrial fibrillation improves the symptoms and probably slows the progress of heart failure.

The effect of atrial fibrillation on the mortality of patients with heart failure is a controversial subject. The VHeFT-I and VHeFT-II studies found no effect of atrial fibrillation on mortality in patients in NYHA heart failure classes II-III.⁹ In contrast, Middlekauff et al maintained that atrial fibrillation had a negative effect on the prognosis of patients with heart failure and pulmonary wedge pressure <15 mmHg.¹⁰ A study by Stevenson et al found that atrial fibrillation increased mortality and sudden death in patients with a severe degree of heart failure who were taking class I antiarrhythmic drugs, whereas it had no effect on the prognosis of patients who were taking angiotensin converting enzyme inhibitors.²⁵ In the SOLVD study it was proved that atrial fibrillation, in patients with asymptomatic or symptomatic heart failure, increased overall mortality by 34% (due to a 42% increase in deaths from pump failure) but did not affect the risk of death from arrhythmia.²³

However, it is not known whether atrial fibrillation contributes to the increase in mortality or is simply an indicator of more serious heart disease. It is likely that the patients' haemodynamic deterioration, the increased risk of thromboembolic episodes and the proarrhythmic action of antiarrhythmic drugs, especially those in class I, all contribute to the increase in mortality.

Of the available antiarrhythmic drugs, only amiodarone and dofetilide have been shown not to increase mortality in patients with heart failure.^{26,27} In addition, those drugs have been found to increase the probability of conversion to sinus rhythm, while patients who are converted have better survival than those who remain in atrial fibrillation. In particular, the DIA-

MOND study, in which patients took dofetilide, showed that the mortality of heart failure patients in sinus rhythm was 40% lower than in those who remained in atrial fibrillation.²⁸ Similar conclusions were reached in the CHF-STAT study, where the mortality of patients who converted to sinus rhythm after taking amiodarone was significantly lower than in those who did not.²⁹

Recent data from the Framingham study indicate that the appearance of heart failure in patients with atrial fibrillation during a 5.6-year follow up period was accompanied by an increase in the multivariate adjusted hazard ratio by 2.7 times in men and 3.1 times in women.³⁰ Conversely, if atrial fibrillation occurs in patients with heart failure the multivariate adjusted hazard ratio increased by 1.6 times in men and 2.7 times in women. Specifically, in men with atrial fibrillation, the mean survival was 1.4 years for patients with pre-existing heart failure at the time the arrhythmia was diagnosed, 2.1 years for those who developed heart failure later and 6.6 years for those who had no heart failure.

These data are in conflict with those from the AFFIRM and RACE studies, which did not find any improvement in the survival of patients who maintained sinus rhythm.^{31,32} In the AFFIRM study it was investigated whether the restoration and preservation of sinus rhythm reduced mortality, compared with control of heart rate and accompanying anticoagulant medication in hypertensive or coronary heart disease patients with atrial fibrillation. The study found no difference in 5-year survival between patients whose heart rate was successfully controlled and who received anticoagulants, compared to those who were cardioverted to sinus rhythm. In fact, the latter patients needed more hospitalisations.³¹ However, it should be stressed that only 22.3% of the patients in the study had heart failure, while the authors recommended that control of the ventricular response to atrial fibrillation should be preferred to cardioversion in the elderly, in patients with coronary artery disease and in patients who do not have heart failure. Perhaps a future meta-analysis of the AFFIRM study, or a newer study, such as the AF-CHF study that is currently in progress, may be able to offer more information, especially concerning patients with atrial fibrillation and heart failure.³³

Treatment of atrial fibrillation in patients with heart failure

The effective treatment of atrial fibrillation in patients with heart failure is essential, not only because it

relieves the symptoms of the arrhythmia and reduces the risk of thromboembolic events, but because it also improves the symptoms and probably the prognosis of the heart failure itself. However, though atrial fibrillation and heart failure often coexist, in most studies of atrial fibrillation patients with heart failure are excluded and for this reason there is a lack of clinical studies to guide treatment.

It is commonly accepted that the treatment of both paroxysmal and chronic atrial fibrillation requires the optimum treatment of heart failure. Reduction of filling pressure and of neurohormonal stimulation can help in the spontaneous cardioversion of paroxysmal atrial fibrillation and in the control of heart rate in both the paroxysmal and the persistent form of the arrhythmia. Conversely, the effective treatment of heart failure may not be feasible if the heart rate is not controlled or sinus rhythm is not restored.

The cardioversion of atrial fibrillation in comparison with the pharmaceutical control of heart rate appears to have a superior effect on exercise capacity but is associated with a greater number of hospitalisations, whereas both strategies lead to an equal improvement in the patients' symptomatology.^{31,32}

An attempt to restore sinus rhythm should be made in the younger patient who has a shorter history of arrhythmia and does not have a significantly large left atrium. Repeat electrical cardioversion shocks may be administered to patients who have remained in sinus rhythm for a long time following a previous cardioversion and who show clear haemodynamic improvement.

In elderly patients with heart failure and chronic atrial fibrillation, who have a small probability of maintaining sinus rhythm after cardioversion, medication for rate control is recommended along with anticoagulant therapy.

For patients with reduced left ventricular function the drugs of first choice are considered to be β -blockers, if there are no contraindications. Digitalis is indicated for patient who cannot tolerate β -blockers, while it is not clear whether it offers an additional benefit to patients who are already taking β -blockers without side effects.

In cases where satisfactory rate control is infeasible and attempts at cardioversion are unsuccessful, the recommended treatment is ablation of the atrioventricular node and implantation of a permanent pacemaker. Especially in patients with severe heart failure and chronic atrial fibrillation, biventricular pacing seems to be an acceptable treatment, even though it has produced conflicting results.³⁴⁻³⁶

Also, pulmonary vein ablation for the treatment of atrial fibrillation, which until recently concerned only patients with normal systolic left ventricular function, has started to be applied in patients with heart failure and seems to be a safe and reliable treatment.³⁷

Finally, it is important to stress that effective treatment of atrial fibrillation may be achieved only with the simultaneous treatment of heart failure, and vice versa: satisfactory management of atrial fibrillation is essential for the optimum treatment of heart failure.

References

- Kannel WB, Abbot RD, Savage DD, McNamara PM: Epidemiological features of chronic atrial fibrillation. *N Engl J Med* 1982; 306: 1018-1022.
- Krahn AD, Manfreda J, Tate RB, Mathewson FAL, Cuddy ET: The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba follow-up study. *Am J Med* 1995; 98: 466-484.
- Onundarson PT, Thorgeirson G, Jonmundsson E, Sigfusson N, Hardarson TH: Chronic atrial fibrillation-epidemiological features and 14-year follow-up: a case control study. *Eur Heart J* 1987; 8: 521-527.
- Garg R, Packer M, Pitt B, Yusuf S: Heart failure in the 1990s: evolution of a major public health problem in cardiovascular medicine. *J Am Coll Cardiol* 1993; 22 (4 Suppl A): 3A-5A.
- Jordaens L, Trouerbach J, Calle P, et al: Conversion of atrial fibrillation to sinus rhythm and rate control by digoxin and comparison to placebo. *Eur Heart J* 1997; 18: 643-648.
- Swedberg K, Idanpaan Heikila U, Remes J, CONSENSUS trial study group: Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987; 316: 1429-1435.
- Parker M, Bristow MR, Cohn JN, et al: The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. US Carvedilol Heart Failure Study Group. *N Engl J Med* 1996; 334: 1349-1355.
- Johnstone D, Limacher M, Rousseau M, et al, and the SOLVD investigators: Clinical characteristics of patients in studies of left ventricular dysfunction (SOLVD). *Am J Cardiol* 1992; 70: 894-900.
- Carson PE, Johnson GR, Dunkman WB, et al; eFT VA Cooperative Studies Group: The influence of atrial fibrillation on prognosis in mild to moderate heart failure. The V-HeFT Studies. *Circulation* 1993; 87(Suppl VI): 102-110.
- Middlekauff HR, Stevenson WG, Stevenson LW: Prognostic significance of atrial fibrillation in advanced heart failure. A study of 390 patients. *Circulation* 1991; 84: 48-58.
- Benjamin EL, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA: Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *J Am Med Assoc* 1994; 271: 840-844.
- Kannel WB, Wolf PA, Benjamin EJ, Levy D: Prevalence, incidence, prognosis and predisposing conditions for atrial fibrillation: Population-based estimates. *Am J Cardiol* 1998; 82: 2N-9N
- Opasich C, Fedo O, Riccardi PG, et al: Concomitant factors of decompensation in chronic heart failure. *Am J Cardiol* 1996; 78: 354-357.
- Grogan M, Smith HC, Gersh BJ, Wood DL: Left ventricular dysfunction due to atrial fibrillation in patients initially believed to have idiopathic dilated cardiomyopathy. *Am J Cardiol* 1992; 69: 1570-1573.
- Van Den Berg MP, Tuinenberg AE, Crijns HJGM, Van Gelder IC, Gosselink ATM, Lie KI: Heart failure and atrial fibrillation: current concepts and controversies. *Heart* 1997; 77: 309-313.
- Ravelli F, Allessie MA: Atrial stretch decreases refractoriness and induces atrial fibrillation in the isolated rabbit heart. *Circulation* 1995; 92 (Suppl I): 754.
- Sanders P, Morton JB, Davidson NC, et al: Electrical remodeling in congestive heart failure. Electrophysiological and electroanatomic mapping in humans. *Circulation* 2003; 108: 1461-1468.
- Shi Y, Li D, Tardif JC, Nattel S: Enalapril effects on atrial remodeling and atrial fibrillation in experimental congestive heart failure. *Cardiovasc Res* 2002; 54: 456-461.
- Wijffels MCEF, Kirchhof CJHJ, Dorland R, Allessie MA: Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation* 1995; 92: 1954-1968.
- Manios EG, Kanoupakis EM, Chlouverakis GI, Kaleboubas MD, Mavrakis HE, Vardas PE: Changes in atrial electrical properties following cardioversion of chronic atrial fibrillation: relation with recurrence. *Cardiovasc Res* 2000; 47: 244-253.
- Vardas PE, Manios EG, Kanoupakis EM, Dermitzaki DN, Mavrakis HE, Kallergis EM: Atrial defibrillation threshold in humans minutes after atrial fibrillation induction. 'A stitch in time saves nine'. *Eur Heart J* 2001; 20: 1613-1617.
- Clark DM, Plumb VJ, Epstein AE, Kay GN: Hemodynamic effects of an irregular sequence of ventricular cycle lengths during atrial fibrillation. *J Am Coll Cardiol* 1997; 30: 1039-1045.
- Dries DL, Exner DV, Gersh MB, et al: Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. *J Am Coll Cardiol* 1998; 32: 695-703.
- Shinbane JS, Wood MA, Jensen DN, Ellenbogen KA, Fitzpatrick AP, Scheinman MM: Tachycardia-induced cardiomyopathy: a review of animal models and clinical studies. *J Am Coll Cardiol* 1997; 29: 709-715.
- Stevenson WG, Stevenson LW, Middlekauff HR, et al: Improving survival for patients with atrial fibrillation and advanced heart failure. *J Am Coll Cardiol* 1996; 28: 1458-1463.
- Amiodarone Trials Meta-analysis Investigators: Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomized trials. *Lancet* 1997; 350: 1417-1424.
- Torp-Pedersen C, Moller M, Bloch-Thomsen PE, et al: Dofetilide in patients with congestive heart failure and left ventricular dysfunction. *N Engl J Med* 1999; 341: 857-865.
- Pedersen OD, Bagger H, Keller N, et al: Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function. A DIAMOND sub-study. *Circulation* 2001; 104: 292-296.

29. Deedwania PC, Singh BN, Ellenbogen KA, Fisher S, Fletcher R, Singh SN: Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation. *Circulation* 1998; 98: 2574-2579.
30. Wang TJ, Larson MG, Levy D, et al: Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: The Framingham heart study. *Circulation* 2003; 107: 2920-2925.
31. The AFFIRM investigators, A comparison of rate control, rhythm control in patients with atrial fibrillation: *N Engl J Med* 2002; 347: 1825-1833.
32. Van Gelder IC, Hagens VE, Bosker HA, et al; Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group: A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002; 347: 1834-1840.
33. Rationale, design of a study assessing treatment strategies of atrial fibrillation in patients with heart failure: the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial: *Am Heart J* 2002; 144: 597-607.
34. Brignole M, Menozzi C, Gianfranchi L, et al: Assessment of atrioventricular junction ablation and VVIR pacemaker versus pharmacological treatment in patients with heart failure and chronic atrial fibrillation. *Circulation* 1998; 98: 953-960.
35. Leon AR, Greenberg JM, Kanuru N, et al: Cardiac resynchronization in patients with congestive heart failure and chronic atrial fibrillation. *J Am Coll Cardiol* 2002; 39: 1258-1263.
36. Leclercq C, Walter S, Linde C, et al: Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. *Eur Heart J* 2002; 23: 1780-1788.
37. Chen MS, Marrouche NF, Khaykin Y: Pulmonary vein isolation for the treatment of atrial fibrillation in patients with impaired systolic function. *J Am Coll Cardiol* 2004; 43: 1004-1009.