Atrial fibrillation and cardiac resynchronization therapy: the MASCOT study

Luigi Padeletti\textsuperscript{a,}\textsuperscript{*}, Nicola Musilli\textsuperscript{a}, Maria Cristina Porciani\textsuperscript{a}, Andrea Colella\textsuperscript{a}, Luigi Di Biase\textsuperscript{b}, Giuseppe Ricciardi\textsuperscript{a}, Paolo Pieragnoli\textsuperscript{a}, Antonio Michelucci\textsuperscript{a}, GianFranco Gensini\textsuperscript{a}

\textsuperscript{a}Institute of Internal Medicine and Cardiology, University of Florence, Florence, Italy

\textsuperscript{b}Cardiovascular Institute, University of Bari, Bari, Italy

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**Abstract** Atrial fibrillation (AF) and congestive heart failure (CHF) share several characteristics and often coexist in the same patient. Both are responsible for significant morbidity and mortality, are increasing in prevalence, and are major sources of health expenditure. The Management of Atrial fibrillation Suppression in AF-HF Comorbidity Therapy (MASCOT) study is a European, single-blind, prospective, controlled, multicentre, randomized clinical trial designed to examine whether adding the AF Suppression\textsuperscript{TM} Algorithm to cardiac resynchronization therapy (CRT) improves the prognosis of patients with CHF. The patients will be randomly assigned to a CRT-only group, with the AF Suppression\textsuperscript{TM} algorithm programmed OFF (control group), versus a CRT + AF Suppression\textsuperscript{TM} group, with the algorithm programmed ON (treatment group). The primary study endpoint is development of permanent AF, and secondary endpoints are safety of the AF Suppression\textsuperscript{TM} algorithm, and evolution of multiple clinical variables over 24 months of follow-up. CRT combined with a refined atrial tachyarrhythmia prevention pacing algorithm may represent a major advance in the management of AF and CHF by electrical stimulation.

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**Introduction**

In 1628, William Harvey first described the relation between atrial and ventricular contractions:

"From these and other observations I am convinced that the motion of the heart is as follows: first the auricle contracts, and this forces the abundant blood it contains as the cistern and reservoir of the veins, into the ventricle. This being filled, the heart raises itself, makes its fibres tense, contracts, and beats. By this beat it at once ejects into the arteries the blood received from
the auricle. These two motions, one of the auricles, the other of the ventricles, are consecutive, with a rhythm between them” [1]. Three centuries later Gesell showed the sudden fall in blood pressure produced by the induction of atrial fibrillation (AF) in dogs [2]. When sinus rhythm was restored blood pressure returned to its original value.

AF and congestive heart failure (CHF) share several characteristics and often coexist in the same patient. Both are responsible for significant morbidity and mortality, are increasing in prevalence, and are major sources of health expenditure. Furthermore, CHF is an important cause of AF and, conversely, AF can exacerbate CHF.

Haemodynamic changes due to atrial fibrillation

The development of AF can adversely affect cardiac function by (1) loss of atrial systole, (2) an increase in ventricular rate, (3) an irregular rhythm, (4) loss of physiological control of heart rate, and (5) the development of tachycardia-related contractile dysfunction, known as tachycardia-induced cardiomyopathy [3–6]. As a result, left ventricular ejection fraction, cardiac output, exercise capacity and peripheral flow decrease, exacerbating symptoms and lowering functional capacity [7–11]. AF may also decrease blood pressure and impair renal perfusion and function. Thus, AF may cause or aggravate CHF [12,13].

Other adverse consequences of atrial fibrillation

The development of AF may have indirect, though serious adverse consequences. In particular, the need to suppress AF may lead to the prescription of drugs with unfavourable effects on survival in CHF [14], and AF in CHF is associated with a higher risk of thromboembolism [15]. With respect to the cumulative effects of AF and CHF, data are conflicting. AF has been reported to have deleterious [16–18], neutral [19,20], or positive [21,22] consequences on survival in patients with CHF. In the large, prospective, community-based Framingham Heart Study, patients with AF or CHF who developed the other condition had a significantly lower survival than patients who did not [23]. It is, therefore, clear that the prevention of AF in patients suffering from CHF is an important treatment strategy to explore.

Heart failure as a cause of atrial fibrillation

Congestive heart failure is a condition which predisposes to the development of AF via a variety of pathophysiological mechanisms, including atrial stretch, activation of the sympathetic nervous system, and structural changes in the atrial myocardium. An increase in atrial pressure in the isolated rabbit heart significantly increased the vulnerability to AF, and was closely correlated with a shortening of the atrial effective refractory period [24]. In dogs, left atrial dilatation by inflation of a balloon catheter shortened the atrial effective refractory period and increased the vulnerability to arrhythmias [25]. In humans, the effect of atrial pressure on atrial refractoriness was studied by varying the atrioventricular (AV) interval during AV sequential pacing. While some investigators reported a prolongation of the atrial refractory period in response to a rise in intra-atrial pressure [26,27], others observed either a shortening or no change, depending on the time-course of the changes in pressure [28,29].

In dogs, CHF causes interstitial fibrosis, a substrate for localised conduction abnormalities, including unidirectional slowing or block, and for the initiation and sustenance of atrial reentrant arrhythmias [30]. The neuro-hormonal activation that accompanies heart failure also contributes to the development of atrial arrhythmias. Sympathetic activation can have profound electrophysiological effects, not only on the atrial substrate, but also on foci capable of triggering atrial arrhythmias [31], for instance in the ligament of Marshall, a well-known potential source of AF sensitive to sympathetic stimulation [32].

Pacing to prevent atrial fibrillation

Atrial pacing may prevent the onset of AF by (a) preventing bradycardia and bradycardia-induced dispersion of refractoriness, which facilitate paroxysmal AF, (b) suppressing or reducing the number of premature atrial contractions that initiate reentry and predispose to AF, and (c) preserving AV synchrony [33]. Various atrial pacing algorithms have been developed to prevent recurrences of AF. Distinct functions of these algorithms can generally be classified as (1) circadian rhythm variations, (2) dynamic rate overdrive pacing, (3) overdrive suppression of ectopic activity after atrial premature events, and (4) prevention of (a) short long cycles, (b) early reinitiation of AF after
convention to sinus rhythm, and (c) exercise-induced AF [34].

The new, rate-adaptive AF Suppression™ atrial pacing algorithm (St. Jude Medical, Sylmar, CA) was designed to provide a high percentage of atrial paced events, while allowing for physiological circadian variations in heart rate. The algorithm increases the pacing rate when the native rhythm emerges and, periodically, slows the rate gradually in search of intrinsic atrial activity (see article by A. Schuchert in this issue [35]). The Atrial Dynamic Overdrive Pacing Trial (ADOPT), designed to assess the clinical efficacy and safety of the AF Suppression™ algorithm in patients with paroxysmal AF, sick sinus syndrome and an indication for permanent pacing, demonstrated that overdrive atrial pacing with this algorithm was safe and decreased the symptomatic AF burden in the patient population studied [36] which was not similar to that anticipated in the MASCOT study. ADOPT included patients with sino-atrial node disease while MASCOT patients will be in heart failure. Despite this difference the results of ADOPT suggest possible value in pursuing evaluation of the AF suppression™ algorithm in heart failure patients who have received resynchronization therapy.

Cardiac resynchronization therapy

In the last decade, biventricular pacing, also known as cardiac resynchronization therapy (CRT), has emerged as an effective therapeutic complement to drug therapy in a subset of patients with CHF refractory to optimal medical management. Approximately 30% of patients in New York Heart Association (NYHA) heart failure functional class III or IV have a prolonged PR interval, or QRS duration, or both, which are independent predictors of mortality [37–39]. These electrical abnormalities cause desynchronized cardiac contractions, impair ventricular function and worsen long-term prognosis. The aim of cardiac resynchronization therapy is to restore AV, interventricular, and intraventricular synchrony to correct the abnormal hemodynamics.

Several prospective, randomized clinical trials have confirmed that CRT significantly improves quality of life, increases exercise capacity and left ventricular ejection fraction (LVEF) and reduces the number of hospitalizations for CHF [40–42]. CRT is now a class IIa indication for patients with CHF and inter- or intraventricular conduction defects [43].

The MASCOT study

The Management of Atrial fibrillation Suppression in AF-HF Comorbidity Therapy (MASCOT) study is a single-blind, prospective, multicentre, randomized clinical trial. The study is based in Europe although there will be a few centres included from Asia and the Middle-East. It is the first trial to evaluate whether adding to CRT an atrial pacing algorithm to prevent AF (AF Suppression™ Algorithm, St. Jude Medical, Sylmar, CA) improves the prognosis of patients suffering from CHF.

Patient selection

Patient enrolment began in September 2003 and will end in September 2005. At least 500 patients will be enrolled during that period. This sample size was not determined on the basis of formal calculations, since no pertinent information is available to allow a reliable estimate of the incidence of AF in patients presenting with NYHA functional class III and IV CHF and a wide QRS complex. However, 500 patients will ensure that the data collected are representative of this type of population and produce dependable results upon which to build further trials.

Patients are eligible to participate in the study if they are over 18 years of age and (1) are in NYHA heart failure functional class III or IV despite
optimal conventional medical therapy, (2) have a spontaneous QRS duration ≥ 130 ms and/or a mechanical interventricular delay > 50 ms, (3) have an LVEF ≤ 35%, and (4) have a left ventricular end-diastolic diameter ≥ 55 mm. Patients will not be included in the study if they (1) have suffered from unstable angina or acute myocardial infarction, or have undergone coronary artery bypass surgery or percutaneous coronary interventions within the last 3 months, (2) have permanent AF, or (3) are pregnant or have a life expectancy < 6 months.

Study design, randomization and protocol

Patients who have consented to participate in the study will undergo a baseline evaluation, followed, within one month, by the implantation of a CRT system. After implantation of the system and before their discharge from the hospital, the patients will be randomly assigned to a CRT-only group, with the AF Suppression™ algorithm programmed OFF (control group), versus a CRT + AF Suppression™ group, with the algorithm programmed ON (treatment group). In the treatment group, the pulse generator will pace consistently at a rate just above the intrinsic atrial rate (dynamic atrial overdrive). After their discharge from the hospital, the patients will be evaluated at follow-up visits scheduled at 6, 12, 18 and 24 months (Fig. 1). They may also be instructed to report at 1 month and 3 months after CRT system implantation, depending on the type of device implanted.

Study outcome measures

The primary study endpoints are (1) incidence of permanent AF during follow-up and (2) prevalence of permanent AF at 12 and 24 months. Secondary outcome measures include all other adverse events, related or unrelated to the AF Suppression™ algorithm or CRT system, and the evolution of multiple clinical variables (Table 1).

Conclusions

Together, AF and CHF create a vicious circle in which CHF promotes AF, and AF aggravates CHF. The haemodynamic benefits conferred by CRT may produce anatomical, functional and neuroendocrine changes which increase the likelihood of maintaining sinus rhythm. CRT combined with a refined atrial tachyarrhythmia prevention pacing algorithm may represent a major advance in the management of AF and CHF by electrical stimulation. MASCOT has been designed to determine whether the addition of such algorithm to CRT has remedial effects on the long-term outcomes of patients suffering from CHF.

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### Table 1: Outcome measures of MASCOT trial

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
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<tr>
<td>• Incidence of permanent AF</td>
<td>• Number of hospitalizations for AF and/or CHF</td>
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<tr>
<td>• Prevalence of permanent AF at 12 and 24 months</td>
<td>• Number of cardioversions</td>
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<td>• Number and total duration of device automatic mode switches</td>
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<td>• Number of thromboembolic complications</td>
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<td>• All other adverse events&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>• Overall mortality</td>
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<td>• Left ventricular ejection fraction</td>
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<td>• Left atrial and left ventricular dimensions</td>
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<td></td>
<td>• Severity of mitral regurgitation</td>
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<td></td>
<td>• NYHA heart failure functional class</td>
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<td></td>
<td>• Quality of life (Minnesota Living With Heart Failure questionnaire)</td>
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<tr>
<td></td>
<td>• Spontaneous QRS complex duration</td>
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<tr>
<td></td>
<td>• Resynchronization system activity log data</td>
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<sup>a</sup> Related or unrelated to AF Suppression™ algorithm or CRT system.
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