

# Atrial Fibrillation Complicating Congestive Heart Failure: Electrophysiological Aspects And Its Deleterious Effect On Cardiac Resynchronization Therapy

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## Abstract

More successful recognition and treatment of cardiovascular risk factors and diseases continues to decrease mortality and increase the proportion of elderly population. Therefore, there are more people with increased risk of developing heart failure and atrial fibrillation in the course of their lives. Atrial fibrillation (AF) can complicate the course of congestive heart failure (HF) leading to acute pulmonary edema. The prevalence of AF, in patients with heart failure, increases with the severity of the disease, reaching up to 40% in advanced cases. In these HF patients, AF is an independent predictor of morbidity and mortality increasing the risk of death and hospitalization. Despite the excellent results obtained with different drugs, the optimal medical treatment can fail in the intention to improve symptoms and quality of life of patients with severe HF. Thus, the necessity to use cardiac devices emerges facing the failure of optimal medical treatment in order to achieve hemodynamic improvement and correction of the physiopathological alterations. Cardiac resynchronization therapy (CRT) can reduce the inter-ventricular and intraventricular mechanical dissynchrony in HF patients. It has been shown that CRT increases the left ventricular filling time, decreases septal dissynchrony, mitral regurgitation, and left ventricular volumes allowing a hemodynamic improvement. However, the development of AF in this setting can avoid the beneficial effects of CRT. Therefore, this manuscript will review the available data on this topic, the electrophysiological aspects of AF, to determine what can be done in the event of an AF complicating congestive HF in CRT patients.

## Introduction

Patients with heart failure are at increased risk of developing atrial fibrillation (AF), despite medical improvements made in recent years. AF can complicate the course of heart failure (HF) leading to worsen of HF symptoms and acute pul-

monary edema.<sup>1-6</sup> There are several changes that predispose aging patients to develop AF. There is an increasing prevalence of left ventricular wall hypertrophy in aging population.<sup>7</sup> The resulting left ventricular diastolic dysfunction with aging may increase the size of the left atrium through an increase in filling pressures predisposing elderly

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patients to develop AF. There are also additional changes in the atria which facilitate the development of AF. Some investigators have observed that normal histological changes in the atrial muscle occur with advancing age which may set the milieu for AF to develop in elderly patients.<sup>8-14</sup>

Despite the excellent results obtained with different drugs, the optimal medical treatment can fail in the intention to improve symptoms and quality of life of patients with severe HF. Thus, the necessity to use cardiac devices emerges facing the failure of optimal medical treatment in order to achieve hemodynamic improvement and correction of the physiopathological alterations. Cardiac resynchronization therapy (CRT) can reduce the inter-ventricular and intraventricular mechanical dyssynchrony in HF patients with left bundle branch block. It has been shown that CRT increases the left ventricular filling time, decreases septal dyssynchrony, mitral regurgitation, and left ventricular volumes allowing a hemodynamic improvement. However, AF can avoid these beneficial effects of CRT through the loss of synchronization between fibrillating atria and ventricular contraction, the irregularity of the ventricular rhythm and the frequently rapid ventricular response rate.<sup>1-3</sup> Therefore, this manuscript will review the available data on this topic, the electrophysiological aspects of AF, to determine what can be done in the event of an AF complicating congestive HF in CRT patients.

### **Atrial fibrillation complicating congestive heart failure**

The prevalence of AF, in patients with HF, increases with the severity of the disease, reaching up to 40% in advanced cases. In these HF patients, AF is an independent predictor of morbidity and mortality increasing the risk of death and hospitalization in 76%.<sup>4-6</sup> More successful recognition and treatment of cardiovascular risk factors and diseases continues to decrease mortality and increase the proportion of elderly population. Therefore, there are more people with increased risk of developing HF and AF in the course of their lives.

There are only few studies on the electrophysiological aspects of AF in congestive HF patients. Despite the clinical implications of AF in HF, the reasons for its high prevalence are not clearly understood. Atrial enlargement is recognized to

play an important role in the development of AF in HF patients. However, the atrial electrophysiological characteristics that predispose to AF in patients with chronic HF have been scantily determined. Studies of atrial electrical remodeling, that is observed as a result of sustained AF, have provided some insights into the changes in atrial electrophysiology that maintain the arrhythmia,<sup>15,16</sup> however, it does not explain the nature of the underlying substrate that leads to AF in chronic HF. Animal studies of atrial electrical remodeling in chronic HF have demonstrated discrete regions of slow conduction associated with the development of interstitial fibrosis but without apparent change in atrial effective refractory periods.<sup>17</sup> Sanders et al<sup>18</sup> demonstrated by electrophysiological and electroanatomic mapping in patients with congestive HF that they have significant atrial remodeling characterized by anatomic and structural changes. These changes included atrial enlargement, regions of low voltage, and scarring; abnormalities of conduction, including widespread conduction slowing and anatomically determined conduction delay and block. They also observed increased refractoriness; and sinus node dysfunction. These abnormalities encountered in their study were associated with an increased inducibility and sustainability of AF and may be responsible in part for the increased incidence of atrial arrhythmias in patients with congestive HF.<sup>18</sup>

AF is a common arrhythmia, and its prevalence in patients with HF increases with aging and the severity of the disease. The process of aging and its effect on the histological appearance of the conduction system of the heart have been scantily described. It was reported that AF in some aged patients was associated with loss of muscle fibers in the sinoatrial node and its approaches without any clear pathological cause,<sup>8</sup> while others have shown degenerative changes in the conduction system with age.<sup>19</sup> The increase in prevalence of AF in older persons has been reported to be associated with degeneration of the atrial muscle in pathological studies. It was demonstrated in well designed studies, that there is clear evidence in the human atrial muscle of age-related electrical uncoupling of the side-to-side connections between bundles, related to the proliferation of extensive collagenous tissue septa in intracellular spaces.<sup>20,21</sup>

### **Electrophysiological aspects of atrial fibrilla-**

tion Structural and anatomic abnormalities of the atria were observed in patients with congestive HF and a strong predisposition to develop AF. There is interesting information regarding the electrophysiological and electroanatomic remodeling of the atria in patients with chronic HF.<sup>18</sup> It was demonstrated that patients with chronic HF and no prior atrial arrhythmias have significant atrial remodelling characterized by anatomic and structural changes, abnormalities of conduction, including widespread conduction slowing and anatomically determined conduction delay and block.<sup>18</sup> Despite the fact that the HF patients had no prior atrial arrhythmias in that study, the electrophysiological abnormalities were associated with an increased inducibility and sustainability of AF.<sup>18</sup> Pathological studies of the atria in chronic HF have shown that structural abnormalities such as interstitial fibrosis, cellular hypertrophy, and degeneration are present.<sup>17, 22, 23</sup> Atrial fibrosis has been demonstrated in the atria of patients with chronic HF due to prior myocardial infarction and also from those with idiopathic chronic HF.<sup>23</sup> Atrial arrhythmias themselves may result in structural changes.<sup>24</sup> The substrate for AF in patients with chronic HF may be due to structural abnormalities and conduction delay rather than changes in refractoriness as occurs in remodeling due to rapid atrial rates.

The electrophysiological mechanism of AF is considered to be either a spiral wave with a continuously changing activation wavefront pattern, random multiple independent reentrant wavelets wandering in the atria around arcs of refractory tissue, or accentuation of focal activity originating mainly from the pulmonary veins, superior vena cava, ligament of Marshall, or other sites of the atrium. On the other hand, experimental studies clearly suggest, that overload in ionized calcium in the senescent human atrial myocardial cells may play an important role in arrhythmogenesis.<sup>25,26</sup> The atrial myocardial cells in the elderly appear to be more susceptible to arrhythmias when calcium homeostasis is disturbed and especially under certain conditions that enhance calcium loading. Strong evidence of abnormalities of the conduction system in an apparently healthy elderly population has been demonstrated. Prolongation of the PR interval, high prevalence of atrioventricular nodal and His-Purkinje disease, and unexplained sinus node abnormalities were

consistently found in older apparently healthy individuals.<sup>27-30</sup> Muscle loss with advancing age was found to be accompanied by an increase in fibrous tissue in both the sinoatrial node and the internodal tracts.<sup>9-11</sup> It was strongly suggested that muscle loss and increase of fibrosis in the atria is a slow but continuous process starting around 60 years of age.<sup>8</sup> It was shown that aging has a profound effect on structural changes and electrophysiological properties of the atrium. Fractionated and abnormally prolonged atrial endocardial electrograms were recorded during sinus rhythm in aging patients with paroxysmal AF. These abnormal atrial electrograms may reflect nonsynchronised, delayed local electrical activity through a diseased atrial muscle, which predispose patients to develop AF.<sup>12, 31-33</sup> Indeed, aging has a profound impact on the histological and thus, electrophysiological changes in the human atrial myocardium which contribute to the higher prevalence of AF in the elderly. With a computer model of atrial fibrillation, Moe et al.<sup>34</sup> showed that an atrial disease characterized by short and non-homogeneous atrial refractory periods, associated to intra-atrial conduction disturbances, is considered an important factor in the appearance and maintenance of AF. Non-homogeneity of refractory periods of contiguous cells causes a slower conduction velocity of the stimulus that propagates through partially repolarized cells, allowing the genesis of unidirectional blocks and the appearance of multiple reentries.<sup>34</sup> These findings were later corroborated by other investigators.<sup>35,36</sup> Clinical electrophysiology has identified several atrial features that may lead to the appearance of AF, sometimes with conflicting results. The atrial refractory period and the extent of its dispersion can be determined through the use of programmed atrial stimulation. This method also allows eliciting several abnormal responses of the atrial muscle, such as repetitive atrial firing, fragmented atrial activity, and intra-atrial conduction delay.<sup>37-39</sup> These abnormal responses are considered to indicate the presence of atrial vulnerability and have been found to be related to the initiation and maintenance of AF.<sup>40-42</sup> Therefore, shorter atrial effective refractory periods, greater dispersion of atrial refractoriness, and atrial conduction delays, are of electrophysiological significance in the genesis of AF. The precise electrophysiological and patho-physiological bases for AF initiation and maintenance have not been resolved yet. As newer and more sophisticated technology become available, controversies about AF genesis

have reemerged, which tells us that there is still a lot to learn about this arrhythmia. New advances may be relevant to the ultimate understanding of the mechanisms of AF initiation by the interaction of the propagating wavefronts with anatomic or functional obstacles in their paths.

### Pharmacological measures in atrial fibrillation

Considering the high prevalence of AF in the elderly and its deleterious effect on HF patients, it is very important to maintain sinus rhythm in these already compromised patients. It has been shown by several studies that pharmacological agents are effective in the treatment of AF complicating HF. The angiotensin converting enzyme (ACE) inhibitors produce a decrease in atrial pressure and in left ventricular end diastolic pressure in patients with HF.<sup>43</sup> Therefore, it is possible that these agents could decrease the susceptibility to develop AF simply by decreasing atrial pressure and atrial wall stress and consequently by attenuation of atrial enlargement. However, a decrease in atrial fibrosis was also demonstrated experimentally only with ACE inhibitors despite similar decrease in atrial pressure obtained with hydralazine.<sup>43</sup> Among other potentially beneficial mechanisms of ACE inhibition, a direct antiarrhythmic effect can not be excluded. Even in the absence of HF, it seems that angiotensin II directly contributes to atrial electrical remodelling. The shortening of the atrial refractoriness during rapid atrial pacing is more pronounced in the presence of angiotensin II. However, this electrical change was prevented with a previous treatment with candesartan or captopril.<sup>44</sup> There was a beneficial effect on AF recurrence with irbesartan in patients with persistent AF who underwent electrical cardioversion.<sup>45</sup> When the drug was administered 3 weeks before cardioversion combined with amiodarone, there was a significant decrease in recurrent episodes of AF. The greater benefit of blocking angiotensin II type I receptors occurred during the first 2 months after electrical cardioversion, suggesting an important role of irbesartan in atrial electrical remodelling after cardioversion. It is very interesting to note that the ACE inhibitor is apparently more effective in patients with lesser symptoms.<sup>46</sup> This is probably due to potentially reversible milder structural changes in patients with lesser symp-

toms. Therefore, irbesartan demonstrated an additional positive effect to amiodarone, which is a class III, multichannel ion blocker that significantly prolongs the atrial effective refractory period.

The safety and efficacy of amiodarone was tested in HF patients in the CHF-STAT trial and SCD-HeFT trial.<sup>47,48</sup> The first trial demonstrated the safety profile of amiodarone in HF patients, with a trend to better survival in non-ischemic cardiomyopathy.<sup>47</sup> The latter trial also showed that amiodarone did not influence significantly overall mortality, however, a subgroup analysis showed an increased mortality in NYHA class III HF patients.<sup>48</sup> Amiodarone is a potent atrial antifibrillatory agent, that together with sotalol, quinidine, and verapamil<sup>47-54</sup> were individually found to significantly maintain sinus rhythm compared to placebo, reduce the incidence of the first AF recurrence, and significantly reduce the ventricular rate. However, amiodarone was found to be more effective than sotalol in prolonging time to the first recurrence after DC cardioversion in patients with persistent AF.<sup>47</sup> Although amiodarone was not directly compared to dronedarone yet, relatively similar findings were observed with dronedarone in maintaining sinus rhythm and in reducing ventricular rate during arrhythmia recurrence.<sup>55</sup> Dronedarone, a benzofuran derivative with electro-pharmacologic profile closely resembling that of amiodarone but without its adverse effects is a new, promising class III drug for the treatment of AF.<sup>55</sup> The SAFE-T investigators have demonstrated that amiodarone is superior to sotalol for maintaining sinus rhythm. However, both drugs have similar efficacy in patients with ischemic heart disease.<sup>49</sup> These class III antiarrhythmic drugs seem to exert their beneficial anti-fibrillatory action by active blocking of potassium channels in patients with structural heart disease. Dofetilide and azimilide, newer class III antiarrhythmic drugs, were also tested to convert atrial fibrillation and maintain sinus rhythm.<sup>56-60</sup> Although the anti-arrhythmic efficacy of azimilide was superior to placebo, it was significantly inferior to sotalol in patients with persistent AF and structural heart disease. This modest antiarrhythmic efficacy, in addition to, the high rate of torsade des pointes and marked QTc prolongation, limit azimilide utilization for the therapeutic management of AF.<sup>56</sup> Class IA and IC drugs may cause lethal ventricular arrhythmias, and espe-

cially the latter drugs are generally precluded in ischemic and structural heart disease.

Wachtell et al<sup>61</sup> demonstrated that losartan, an angiotensin receptor blocker (ARB), reduced the incidence of new-onset AF in 33% compared to atenolol despite a similar blood pressure control in both treated groups. In addition, the clinical relevance of preventing new onset AF was clearly demonstrated, since AF was associated with a 2 to 5 fold greater cardiovascular morbidity and mortality, cerebrovascular accidents and hospitalization due to HF. New onset AF was reduced 45% with trandolapril in the TRACE study.<sup>62</sup> A sub-analysis of the SOLVD study showed a 78% reduction of new onset AF with enalapril.<sup>46</sup> It is important to note that both were placebo controlled studies, therefore, it is probable that the antihypertensive effect of the ACE inhibitor contributed to the less incidence of AF decreasing atrial pressure and left ventricular end diastolic pressure. In this regard, the LIFE study showed that high systolic pressure is an independent predictor of the development of new onset AF.<sup>61</sup> The LIFE study showed that patients with AF history had a reduction of 42% in combined end point and cardiovascular morbidity and mortality, with a 45% reduction in the risk of cerebrovascular accidents.<sup>63</sup> A probable explanation of the benefit obtained with losartan, could be the regression of atrial hypertrophy. Ventricular hypertrophy is an important predictor of the development of new onset AF. Patients with left ventricular hypertrophy have atrial enlargement, which is associated with an increased risk of cerebrovascular accidents.<sup>64-67</sup>

The pharmacological treatment of AF still remains a clinical challenge. The ACE inhibitors and ARB agents have demonstrated a significant efficacy in reducing the incidence of AF in HF and hypertensive patients. The relative efficacy and safety of antiarrhythmic drugs over long periods of time limits their usefulness in patients with congestive HF. Advance HF patients with AF may be treated with amiodarone or dofetilide, but most other antiarrhythmic drugs are unsuitable. The class III multichannel blockers appear to exert a better performance in AF patients than other antiarrhythmic classes, and dronedarone seems promising. The relatively high incidence of ventricular arrhythmias and marked QT interval prolongation with

some "pure" class III antiarrhythmic agents limit their utilization for the therapeutic management of AF. Therefore, the pharmacological treatment of AF still remains uncertain, and requires careful and detailed evaluation from a safety perspective.

### Cardiac resynchronization therapy in congestive heart failure

Despite the good results obtained with different drugs in the treatment of HF, the optimal medical treatment can fail in the intention to improve symptoms and quality of life of patients with severe HF. Thus, the necessity to use cardiac devices emerges facing the failure of optimal medical treatment in order to achieve hemodynamic improvement and correction of the physio-pathological alterations. Patients with HF and complete left bundle branch block (LBBB) commonly have an abnormal movement of the interventricular septum that is related with interventricular dissynchrony and the resultant abnormal pressure gradient between the two ventricles.<sup>68-70</sup> Due to this abnormal septal movement, there is an increase in the end systolic diameter of the left ventricle and a decrease in regional septal ejection fraction. Patients with LBBB with or without cardiac disease may show a decrease global left ventricular ejection fraction, a decrease in cardiac output, and dP/dt.<sup>70,71</sup> In addition, in cases of ventricular dissynchrony, the closure of the mitral valve may be incomplete because atrial contraction is not followed by a time-adequate ventricular systole. If this delay is sufficiently long, a ventriculo-atrial pressure gradient is generated which promotes mitral regurgitation in the early phase of diastole. It is easy to imagine that ventricular dissynchrony in HF patients puts the failing heart in additional mechanical disadvantage. By placing pacing electrodes in the coronary sinus, the right ventricular apex, and in the right atrial appendage (Figure 1), CRT can deliver simultaneous electrical stimulation of both ventricles which results in a significant hemodynamic improvement restoring a more homogeneous contraction pattern. Furthermore CRT can adjust bi-ventricular stimulation (simultaneous, anticipated, or delayed) to better synchronization. CRT can reduce the interventricular and intraventricular mechanical dissynchrony produced by LBBB. It has been shown that CRT increases the left ventricular filling time (Figure 2), decreases septal dissynchrony and mitral re-

Table 1

## The benefits of the atrial fibrillation suppression algorithm

**Automatically suppression of paroxysmal and persistent atrial fibrillation**

Significant decrease in symptomatic episodes of atrial fibrillation

Decrease in the need for painful electric cardioversion

Improvement in the quality of life of the patients

Effective and safety

Well tolerated by 97% of the patients

Promotes an atrial stimulation with adequate rates for the patient.

gurgitation (Figure 3), allowing a hemodynamic improvement<sup>72-74</sup> These beneficial hemodynamic changes are already seen in a few days and are followed by chronic adaptations that allow long term benefits. Several longitudinal clinical studies demonstrated beneficial effects of CRT in left ventricular remodeling.<sup>75-78</sup> There was a structural and functional ventricular improvement during CRT. At 3 months, there was a significant improvement in left ventricular ejection fraction, and a significant decrease in end systolic and end diastolic volumes.<sup>75-78</sup> These beneficial effects are, apparently dependent on continuous bi-ventricular stimulation since interruption of electric stimulation produce a progressive but not immediate loss of effect. Therefore, CRT reverts the ventricular reverse remodeling produced by chronic heart failure, and it is suggested that improvement in mechanical synchrony is the predominant mechanism. There are significant hemodynamic beneficial changes produced by CRT that are clearly seen at the clinical level and outcome.

**Atrial fibrillation and cardiac resynchronization therapy**

Various studies have shown that CRT is beneficial to patients with HF in sinus rhythm [79-81]. However, CRT is interrupted in over one-third after successful implantation of a CRT device, and the most common reasons for interruption of CRT are the development of AF (18%) and loss of left ventricular capture (10%) [82]. However, CRT can be re-instituted in a high proportion of patients so that only 5% of patients who successfully undergo implantation of a CRT device permanently lose adequate CRT. About one third of patients do not respond to CRT for varying reasons, these are the so called "non-responders". Some have a complex coronary sinus anatomy that does not allow adequate positioning of the electrode catheter. Others have myocardial scars that do not respond to stimulation. Some other reasons are related to the device itself.<sup>82-85</sup>

Recent studies have also focused on the benefit of CRT to HF patients with chronic AF, since these

Table 2

## Benefits of AV nodal ablation in CRT for HF and atrial fibrillation

**Ensures delivery of resynchronization therapy**

Avoids occurrence of fusion or pseudo-fused beats

Eliminates the risk of rapid ventricular rates

Regularizes the cardiac rate

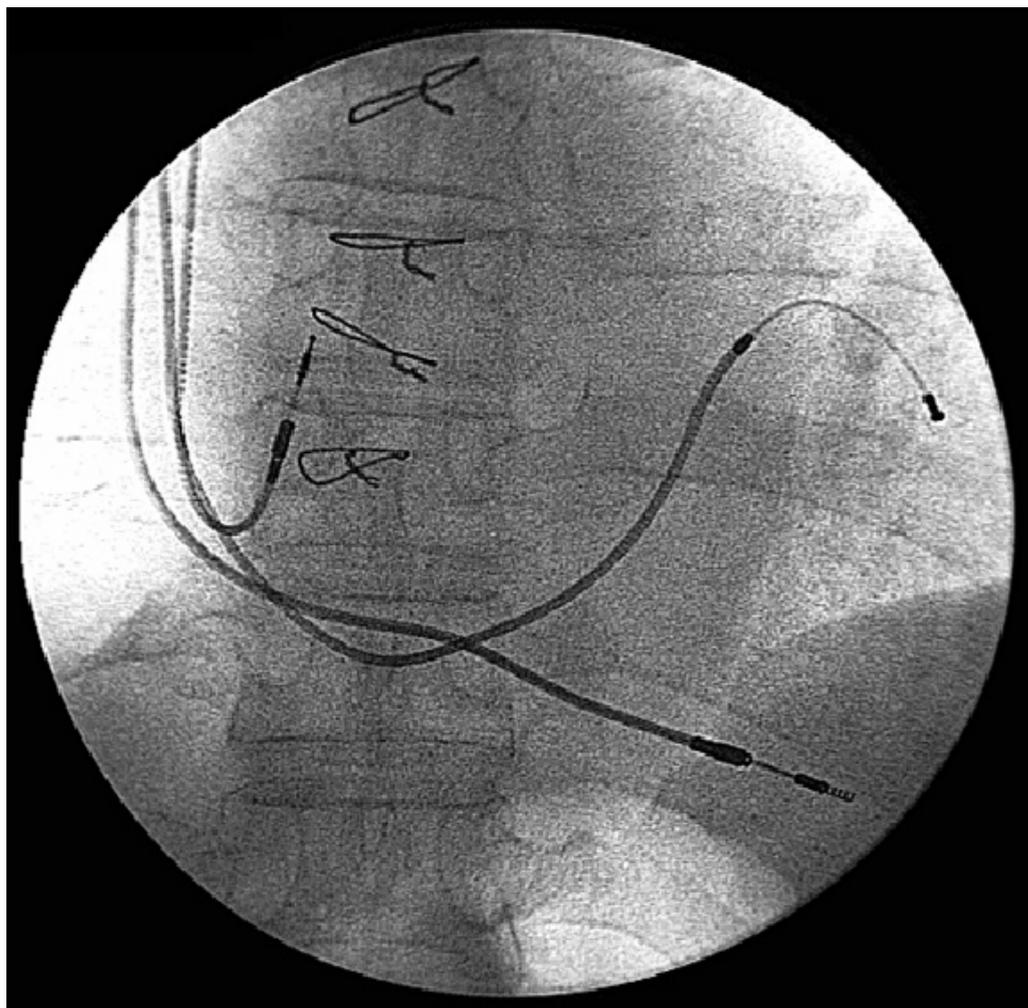
Allows discontinuation of antiarrhythmic therapy

patients have substantially increased morbidity and mortality.<sup>83</sup> These studies showed that patients with AF may benefit from CRT as well.<sup>79-81</sup> <sup>84</sup> In this regard, Leon et al <sup>84</sup> reported improved clinical parameters in 20 patients with chronic AF. In particular the NYHA functional class improved by 29%, the quality of life by 33%, and the LV ejection fraction by 44%. Leclercq et al<sup>81</sup> reported a 10% improvement in six minute walk distance in a substudy of the MUSTIC trial, which is a randomized trial evaluating patients with AF. Kics et al <sup>85</sup> obtained similar results by showing significant improvements in NYHA class, quality of life score, and six minute walk test after six months of CRT. However, on an individual basis, 22% of their patients did not respond to CRT, in line with studies of patients with sinus rhythm.<sup>85</sup> A significantly greater benefit was observed among patients who had an AV node ablation. This may be explained

by the fact that AV node ablation ensures 100% ventricular capture, whereas 100% capture and rate control are difficult to achieve with medical treatment.<sup>84,86</sup> Even with optimized rate control in the non-ablated patients, an average of only 81% ventricular pacing during CRT was obtained, which is not good enough to deliver optimal CRT.

Almost one fifth of patients who undergo successful implantation of a defibrillator capable of delivering CRT experience an AF with a rapid ventricular response, which at least temporarily results in the inability to deliver adequate CRT. Predictors of interruption of CRT as the result of the development of AF in the HF population include a previous history of AF, a relatively slow resting heart rate, and the absence of therapy with both beta-blockers and ACE inhibitors.<sup>83</sup> These findings are consistent with a recent analysis of the SOLVD

**Figure 1:** Catheter electrodes position during CRT. By placing pacing electrodes in the coronary sinus, the right ventricular apex, and in the right atrial appendage, CRT can deliver simultaneous electrical stimulation of both ventricles which results in a significant hemodynamic improvement restoring a more homogeneous contraction pattern.

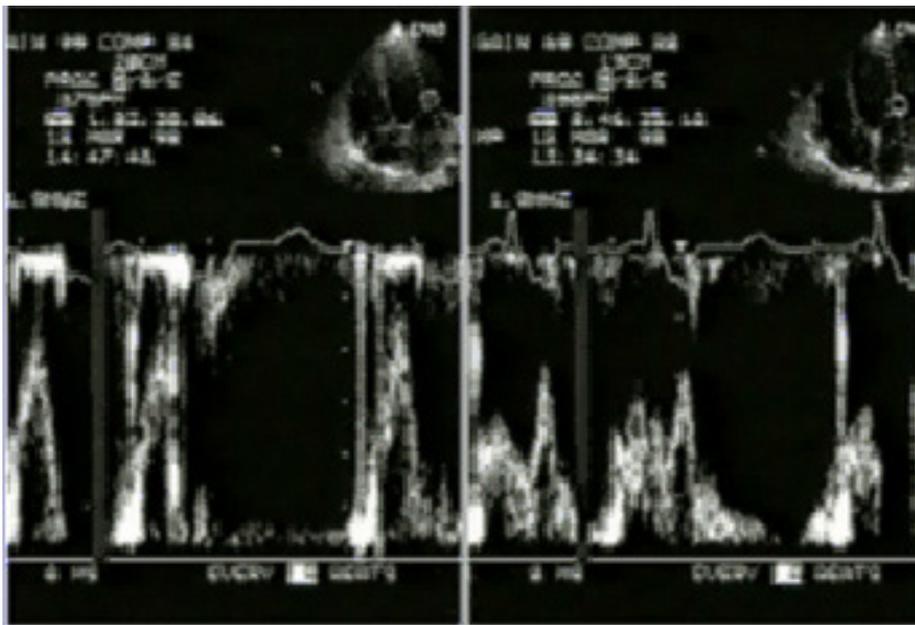


study which found that treatment with enalapril markedly reduces the risk of development of AF in patients with left ventricular dysfunction.<sup>78</sup> Therefore, although it is not clear whether the use of both beta-blockers and ACE inhibitors directly influence the effectiveness of CRT, their use ap-

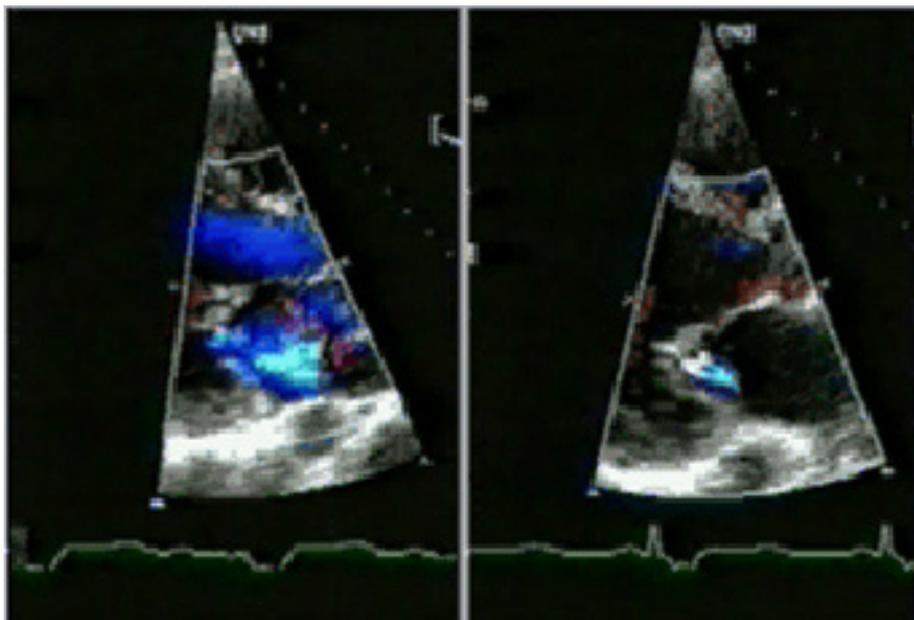
pears to improve the ability to deliver CRT.

Implantable atrial pacemakers and defibrillators can significantly decrease the incidence of AF and also improve quality of life. These implantable devices have an important role in the treatment of AF,

**Figure 9: Transmittal Pulse Wave Doppler Echocardiography.** With the CRT device on, there is an increase and improvement in the left ventricular filling time.



**Figure 3: Transmittal Color Doppler Echocardiography.** With the CRT device on, there is a decrease in mitral regurgitation.



particularly in association with other treatments.<sup>87</sup> It is clear to see that prevention of AF will improve the ability to deliver CRT, and these implantable devices play an important role to achieve this goal. In this regard, it is useful the atrial fibrillation suppression algorithm (AFSA) in dual-chamber permanent pacemakers.<sup>88</sup> It was stated that the AFSA is a stimulation parameter designed specifically to suppress AF. It eliminates the unnecessary rapid stimulation produced by the pacemaker associated to the fixed overdrive stimulation when the patient is at rest. AFSA even performs the overdrive stimulation when the intrinsic atrial rate of the patient increases in response to physical activity (Table 1). It is a valuable tool to apply to paroxysmal and persistent AF in selected patients that need a permanent pacemaker.<sup>88</sup>

### AV node ablation in AF and cardiac resynchronization therapy

A Patients in AF do not have AV synchrony, thus it is not possible to perform a synchronized pacing with adequately programmed AV intervals.<sup>88-91</sup> Therefore, the efficacy of CRT is compromised since adequate capture of biventricular pacing can not be guaranteed. In addition, since AF patients usually have a consistent or intermittent rapid ventricular rate, they require higher pacing rates. Higher pacing rates are not constantly effective because of fused or pseudo-fused ventricular complexes making the percentage of capture inexact, which leads to overestimation of effective CRT capture. It is required an almost maximal and complete biventricular capture to assure an optimal CRT response.<sup>81</sup> The exact treatment of patients with AF undergoing CRT is unclear; concomitant AV node ablation has been proposed to avoid non-capture of pacing during AF. AV node ablation in this setting may be an interesting way of controlling the cardiac rate and reliably delivering CRT (Table 2). On the other hand, it has been suggested that patients may return to sinus rhythm after a certain period of time with CRT, making AV node ablation unnecessary. However, it is unclear whether patients with chronic AF will revert to sinus rhythm after CRT. In this regard, Kíes et al.<sup>85</sup> found in patients with severe HF and chronic AF that CRT improved symptoms, exercise capacity, systolic LV function, and LV reverse remodeling. In addition, left atrial reverse remodeling was observed in this patient popula-

tion. However, these beneficial atrial changes did not restore sinus rhythm in patients with HF with concomitant AF. These findings suggest that AV node ablation should be considered for patients with chronic AF undergoing CRT. There should be a strong effort to prevent AF, since it would significantly improve the ability to deliver CRT in patients with HF. Because patients with slower heart rates are more likely to develop AF, a dual-chamber rate-modulated pacing mode (DDDR) may reduce interruptions of CRT. On the other hand, the search for better pharmacological maneuvers to maintain sinus rhythm should continue to provide the help needed to cardiac devices. The incorporation of the AF suppression algorithm to CRT devices may be very useful in eliminating AF, allowing a better performance of the CRT device without interruption.<sup>86</sup>

The MUSTIC AF trial,<sup>81</sup> the OPSITE trial,<sup>92</sup> and the PAVE trial [93] are the only randomized CRT trials that permitted enrollment of AF patients who underwent AV nodal ablation. The MUSTIC AF trial enrolled patients with persistent AF of at least 3 months duration with spontaneous or induced slow ventricular rate.<sup>81</sup> Most of the patients had slow ventricular rates induced by AV node ablation. These AF patients with slow ventricular rate have a higher grade of ventricular capture and CRT efficacy. The "intention-to-treat" analysis did not find a significant difference in the primary end point: 6 min walking test. This is probably due to the small sample size, and to the fact that only 39 out of 64 patients completed the cross over phase. Nevertheless, this trial demonstrated a positive trend in the secondary end points, namely, NYHA functional class, quality of life, hospitalization for worsening HF, and oxygen consumption. However, this positive trend became statistical significant when only patients with 85% or more biventricular stimulation percentage was included. These patients had significantly left ventricular reverse remodeling. The OPSITE trial<sup>92</sup> had a heterogeneous population, and was also strongly limited by a high percentage of drop-out (32%). Therefore, it only showed a modest effect on quality of life and exercise capacity in patients with CRT and AV node ablation. The PAVE trial demonstrated at 6 months of follow-up that patients with CRT and AV node ablation had significantly increased exercise capacity, quality of life, and left ventricular ejection fraction.<sup>93</sup> A recent observational study<sup>94</sup> with 673 consecutive patients

treated with CRT enrolled 114 AF patients. Only 42% of these AF patients had an adequate biventricular capture despite optimal medical treatment and optimal pacing programming. Therefore, these patients underwent AV node ablation. The final results showed that only the patients with AV node ablation had evidence of reverse remodeling, increased ejection fraction, decreased left ventricular volumes, and improved clinical functional status. In an extension of this study, a much larger multi-center, observational study,<sup>95</sup> Gasparini et al demonstrated in HF patients with permanent AF, that AV node ablation, in addition to CRT, improves long-term overall mortality primarily by reducing HF deaths. Although promising and inspiring, this result comes from a non-randomized study, therefore, well designed and controlled prospective randomized trials are necessary to further confirm these findings.

## Conclusions

The results of several randomized trials demonstrated that CRT devices improve HF symptoms and decrease mortality when the optimal medical treatment fails in severe HF patients. It was demonstrated in patients with permanent AF and CRT that AV node ablation permitted an effective biventricular capture allowing the beneficial effect of CRT. The AV node ablation turns the patient pacemaker-dependent, and allows a complete and consistent CRT without fusion or pseudo-fusion, with a regular cardiac rhythm. AV node ablation, in addition to CRT, improves long-term overall mortality primarily by reducing HF deaths in patients with severe congestive HF and chronic AF. Although promising and inspiring, this result comes from a non-randomized study, therefore, well designed and controlled prospective randomized trials are necessary to further confirm these findings. In the meanwhile, detailed individual evaluation of our HF patients based on scientific evidence will provide us with the best therapeutic decision making for each particular case.

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