Particularities of Biventricular Stimulation in Chagasic Patients

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Summary

Despite the great progress in pharmacological therapy, it remained a challenge to relieve symptoms and improve the survival rate of patients with congestive heart failure secondary to Chagas' disease. The disease is progressive and causes increased morbidity and early death. During the last decade, surgical alternatives such as pacemaker therapy were attempted in order to treat these patients. Due to controversial results, no standard procedure has been established to date. Biventricular pacing, which is achieved by placing a special lead in the coronary sinus system to stimulate the ventricles simultaneously, has become a new promising therapy in heart failure patients. The available results in the literature on biventricular pacing pertain to patients with congestive heart failure due to either idiopathic or ischemic dilated cardiomyopathy. With respect to Chagas' disease etiology, there is no sufficient data to define a procedural strategy for cases with atypical anatomical-pathological structure, causing frequent therapeutic failures. Prospective studies will have to be conducted in order to render this new methodology an appropriate alternative for the treatment of patients in whom heart transplantation is the only alternative therapy.

Key Words

Congestive heart failure, Chagas' disease, biventricular pacing

Introduction

Chagas' disease is characterized by a clear progression of symptoms. The acute phase, usually of little significance, is followed by a variable period of latency. In some patients this is followed by the disease of the viscera, of the heart, and to a lesser degree, of the digestive system. Ever since Carlos Chagas first described the cardiac form of the disease in 1909, many theories have been postulated to explain the development of myocardial lesions. More recently, it became possible to visualize the spread of the inflammatory processes in a non-invasive fashion, using magnetic resonance imaging. For the first time, myocardial biopsy has helped to find the T. cruzi antigen "in vivo" in these patients. This led to the hypothesis that the T. cruzi antigen plays an important role in the development of chronic lesions in the Chagas' disease [1].

Chronic chagasic cardiomyopathy is one of the most frequent indications for pacemaker implantation in Brazil, accounting for up to 70 % of primary pacemaker implantations in some regions. The cardiomyopathy has transformed during its evolution; it is manifested clinically as a number of different anomalies which may appear in isolation or in conjunction. As a characteristic pattern of this pathology, symptoms such as complex polymorphic and multifocal arrhythmias, thromboembolisms (originating mainly from apical aneurysms), and a wide variety of atrioventricular (AV) conduction dysfunctions, with inclusion of the His-Purkinje system, could be observed. If it is not immediately diagnosed and treated, it can cause sudden death. Spread of the disease to the myocardium causes a diffuse, progressive, fibrotic chronic myocarditis, leading to congestive heart failure. Usually, arrhythmias proceed the cardiac insufficiency [2]. About the most important feature of this disease is its evolutionary character, as well as the level of risks

that patients are exposed to. This is a relevant issue, considering that most of the individuals affected are young (between 30 and 40 years old), and still within the productive period of their lives.

Despite the great progress achieved during the 1990's in the available treatments for cardiac insufficiency (which provided an advanced therapeutic arsenal), a great number of patients with dilated cardiomyopathy have had their condition worsen as the disease progressed, resulting in repeated hospitalization and a decline in the quality of life. For this reason, several non-pharmacological procedures have been attempted in order to treat these patients. These have included artificial cardiac pacing (proposed in the early 90's by Hochleitner et al. [3,4] and Brecker et al. [5]), and biventricular stimulation, which was first described by Bakker et al. in 1994 [6]. In this context, the last decade of clinical research has shown a correlation between dilated cardiomyopathy, and both myocardial function and intraventricular conduction dysfunction. It was demonstrated that widened QRS complexes with longer contraction and relaxation times affected the fibers during myocardial action [7]. Such findings initiated clinical research for treating these patients with permanent biventricular pacing by means of a special lead for simultaneous biventricular stimulation that is advanced into the coronary sinus system. Initially, the procedure was marred by technical difficulties. With the recent development of the anatomically adapted leads, problems such as lead displacement, difficulties in lead positioning, and high stimulation thresholds have been largely solved. Since 1994, numerous studies have been performed in centers in Europe and the US, offering promising results. The patients who were studied exhibited improved ejection fraction and systolic volume, as well as significantly diminished mitral regurgitation, with the same left ventricular filling time [8]. Biventricular pacing can be also used to treat chagasic patients, which will be discussed in this article.

Clinical Experience with Dual-chamber Pacing Systems

As most of our patients initially presented with Chagas' etiology, we were able to observe their worsening condition – they exhibited cardiomegaly and NYHA functional class III and IV – and first analyze their survival statistics trends. In 1978, Pimenta et al. [9] demonstrated that the use of an electrical pacemaker had diminished mortality and had provided noticeable improvements in the lives of chagasic patients with AV block.

In the early 1980s we implanted 23 patients, who had complete AV block, with dual-chamber (DDD) pacemakers. This was undertaken in order to increase cardiac output by optimizing the AV coupling interval. Although the patients' conditions first improved, it was not possible to avoid the progression of the disease, and all patients died within a 36-month period.

In the beginning of the 1990's, papers appeared in the literature reporting that cardiac function could be improved in patients with dilated cardiomyopathy and reduced ventricular function, by implanting a DDD pacemaker and programming a short AV delay. However, the required AV delay needed to produce optimal AV synchrony varied from patient to patient. Mitral regurgitation was observed in patients with elevated diastolic left-ventricular pressure. It has been reported that the critical AV delay at which diastolic mitral regurgitation is induced may represent the upper limit of the optimum AV interval. This is possible to assess by simply observing a slightly prolonged AV delay; it determines the interval between the end of the atrial contraction and complete mitral valve closure (diastolic mitral regurgitation duration).

In 1994, following these published guidelines, our group started implanting DDD pacemakers with a short AV interval (100 ms) in five chagasic patients. The best results were achieved in a 71-year-old female with idiopathic dilated cardiomyopathy and left bundle branch block. Four months after pacemaker implantation, the ejection fraction increased from 24 % to 43 %, and the NYHA class improved from III to I. During the same decade, we evaluated 47 chagasic patients with heart failure and AV-block after the implantation of a dual-chamber pacemaker, with the heart rate regulated by Closed Loop Stimulation. The reestablishment of the physiological relationships by this type of sensor promoted a significant improvement in these patients' clinical conditions [10].

Biventricular Pacing

Dilated cardiomyopathy is characterized by structural abnormalities of the ventricular myocardium, which affects the activation and the mechanical contractility of both ventricles. Electrical activation of the ventricular segments may be delayed due to the pathology of the

ventricular conduction system, or to the heterogeneous diffusion of the excitation waves created by the scar tissue. In patients with left-bundle-branch and complete heart block without structural disease, we have observed a diminished left ventricular ejection fraction, associated with ventricular asynchrony [11-13].

Biventricular stimulation was proposed as an option for resynchronizing the ventricles to treat patients with NYHA classes III and IV who suffer from dilated cardiomyopathy. The PATH-CHF trial suggested an improvement in biventricular stimulation with better contractility and pulse pressure [14] when the QRS was above 150 ms. The MUSTIC trial enrolled 58 patients with class III congestive heart failure; patients were randomized into groups with atrial synchronous biventricular stimulation vs. no pacing, and then the groups were reversed. The biventricular group demonstrated significant improvement in exercise tolerance and quality of life. In addition, there were significantly fewer hospitalizations during biventricular pacing [15].

The INSYNC study examined the safety and efficacy of a multisite pacemaker and left-ventricular pacing leads. The system was implanted successfully in 68 patients with NYHA class III or IV congestive heart failure. This study also reported important clinical benefits, including a decrease in mean NYHA functional class, improvement in quality of life scores, and a longer mean distance covered during the 6-minute walk test [16].

The location of the optimal site for left ventricular stimulation, and determining whether biventricular stimulation should be simultaneous or not simultaneous (whether the left ventricle should be stimulated prior to the right ventricle, or at the same time) were still not conclusive. Auricchio et al. provided additional insight into these issues by using data from PATCH-CHF. They found that there may be advantages to non-simultaneous stimulation (left pacing followed by right stimulation) in some patients, and in order to achieve optimal hemodynamics, resynchronizing the right and left ventricles may not be preferable. It was also noted that coordinating movement between the left-ventricular free wall and the septum may be the key, and hemodynamic improvement was greater when stimulating the left ventricular free wall rather than the left ventricular wall.

The question of whether the clinical success of biventricular pacing was dependent on the etiology of the cardiomyopathy was also addressed by the PATH-CHF, MUSTIC and INSYNC trials. All three studies concluded that the response to biventricular stimulation was similar, regardless of whether the cardiomyopathy was due to ischemic or non-ischemic etiology. Recently, Braunschweig et al. reported in an open study that over a mean follow-up time of 291 days, biventricular pacing improved NYHA class, exercise tolerance, and the quality of life significantly in 13 out of 16 patients with severe heart failure and wide QRS complexes [17]. The clinical improvement was accompanied by a significant reduction in hospital care.

Biventricular Pacing and Chagas' Disease

Chronic chagasic cardiomyopathy presents in several evolutionary forms. Clinical syndromes usually develop either together or in isolation. Cardiac arrhythmias occur frequently, in about 50 % of the cases, followed by signs of cardiac insufficiency. The presence of severe ventricular arrhythmias, conduction dysfunction, and cardiac insufficiency provide an unfavorable diagnosis. Sudden death occurs during the most productive phase of these patients' lives [18-21].

The hemodynamic exteriorization of the congestive heart failure with Chagas' etiology is comparable in many ways to dilated cardiomyopathy. Classic therapeutic interventions, with the use of saline restriction, diuretics, and vasodilators, have been routinely used for relieving patients' symptoms, mainly those treated with the associated angiotensin conversion enzyme (ACE) inhibitors. Although we still do not have large studies in this area, there is evidence that these drugs, at least acutely, produce a neuromodulator effect in Chagas' heart disease patients that is comparable to those seen with other cardiac insufficiency etiologies [22,23].

The GESICA study has shown that after a 2-year follow-up period, low doses of amiodarone has decreased mortality as well as the need for hospitalization in heart failure patients, independent of the occurrence of complex ventricular arrhythmias. Approximately 10 % of these patients had Chagas' etiology. In this group of patients, ACE inhibitors have been shown to improve mortality and morbidity in moderate to severe heart failure and in asymptomatic left ventricular dysfunction. Beta blockers further reduce mortality and morbidity. The drug treatment was carefully optimized in a stable dose for all patients in the different trials. In

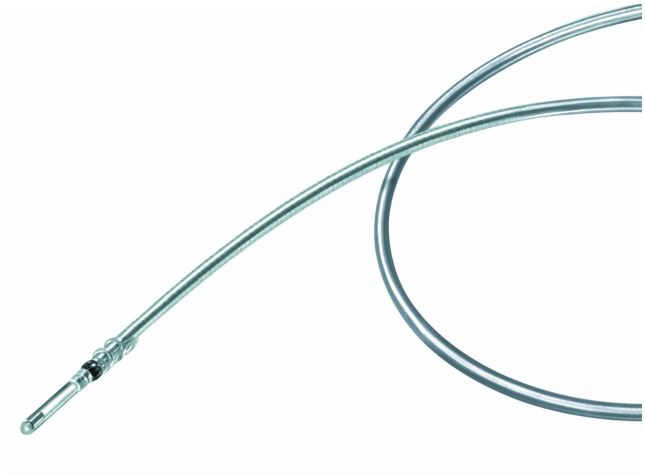

Figure 1. Appearance of the Corox LV (Biotronik, Germany) lead for left ventricular (LV) pacing. The lead was implanted in one of the patients with Chagas' disease treated at our institution, in order to institute atrio-biventricular pacing.

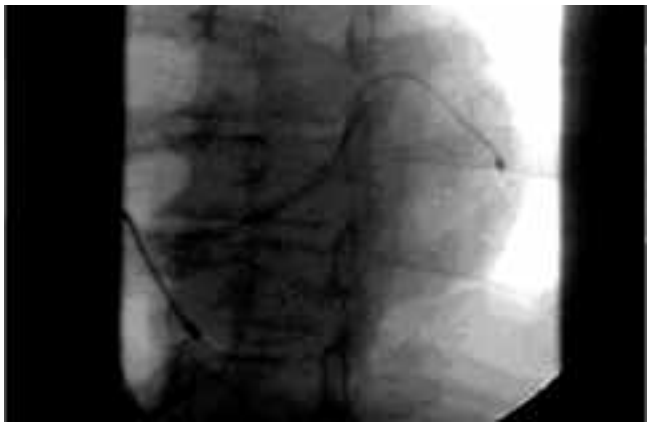

Figure 2. Final positions of the implanted right and left ventricular leads in the studied patient.

spite of the non-invasive pharmacologic agents now available to treat these patients, and the continuous search to find new drugs, more and more patients are re-hospitalized because of acute cardiac insufficiency recurrences [24-27].

Despite the improvements observed during the past decade, the prognosis of patients with advanced heart failure remains poor, and is associated with a poor quality of life. Non-pharmacological options for these patients have been limited, since heart transplantation is restricted by a donor shortage, and since left ventricular support devices are still in the investigational stage. The application of alternative therapies, especially cardiosurgical ones, is based on the extension of high-risk treatments. Heart transplantation is limited due to the scarcity of donors; it is reserved for those patients who have not benefited from alternative therapy. This includes the repair of mitral insufficiency, surgical ventricular remodeling, extreme revascularization, mechanical devices to support circulation, and the combination of pharmacological and non-pharmacological treatments such as ventricular resynchronization [28-30].

Biventricular pacing with desynchronized ventricular activation is a recently developed technique for treating patients affected by heart failure. The interest in this new therapeutic technique is justified because it will only be performed endocardially, without any significant risk to the patient, and will significantly improve the patient's quality of life [16,31].

After the specifically designed coronary sinus leads have become available, we treated one chagasic patient with atrio-biventricular pacing. The Actros DR dual-chamber rate-adaptive pacemaker was implanted together with a Corox LV lead for left ventricular pacing (Figure 1), a standard right ventricular lead, and an atrial lead (products of Biotronik, Germany). To connect the right and left ventricular leads to the single ventricular port of the used pacemaker, the A1-CS-SB adapter was applied (Biotronik). Figure 2 illustrates the final position of the implanted ventricular leads. During the 5-month follow-up period of biventricular pacing, the Minnesota questionnaire score showed a significant improvement in the patient's quality of life compared to the period before pacemaker implantation. Moreover, the use of diuretic and ACE drugs could be reduced to half of the initial doses.

Conclusion

In spite of advances in the medical management of congestive heart failure, a significant number of patients with left ventricular systolic dysfunction still develop severe and medically refractory symptoms. Studies have suggested the possibility that biventricular stimulation may be a good alternative for patients with advanced heart failure and bundle branch block. The data presented here suggest that biventricular pacing,

by correcting intraventricular contractile asynchrony, may contribute to improved ventricular function.

In cases of Chagas' disease, there is little information on this new form of stimulation, which, for the moment, makes it difficult for us to reach a conclusion. Since the disease's behavior is similar to that of dilated cardiomyopathy, we believe that biventricular pacing might be useful for chagasic patients as well. However, in chagasic patients the intraventricular conduction dysfunction affects the right bundle branch and the antero-superior left branch, and its anatomical pathological substrate consists of a progressive diffuse fibrosis.

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