Cardiac resynchronization therapy in patients with congenital heart disease

Resynchronisation cardiaque et cardiopathies congénitales

Jean-Benoit Thambo\textsuperscript{a,*,b,c}, Pierre Dos Santos\textsuperscript{b,c}, Pierre Bordachar\textsuperscript{b,c}

\textsuperscript{a} Département des pathologies cardiaques congénitales du fœtus, de l’enfant et de l’adulte, hôpital cardiologique du Haut-Lévêque, CHU de Bordeaux, avenue de Magellan, 33604 Pessac cedex, France
\textsuperscript{b} Hôpital cardiologique du Haut-Lévêque, 33000 Bordeaux, France
\textsuperscript{c} Université Bordeaux Segalen, 33000 Bordeaux, France

Received 24 February 2011; received in revised form 27 April 2011; accepted 27 April 2011
Available online 2 July 2011

\textbf{KEYWORDS}
Congenital heart disease; Cardiac resynchronization therapy; Heart failure; Ventricular dyssynchrony; Ventricular arrhythmia

\textbf{Summary} Adults with congenital heart lesions constitute a rapidly growing group of patients with cardiovascular disease. This nascent demographic phenomenon is creating major issues concerning the optimal management of these patients, in whom sudden death and progressive heart failure are predominant causes of death. Ventricular dyssynchrony appears to be very common in this population and can appear early in the history of the disease. Recently, cardiac resynchronization therapy (CRT) has emerged as a potential treatment option for patients with congenital heart disease (CHD). In this paper, we review the clinical evidence for the role of CRT in a number of different groups of patients with congenital heart lesions. In particular, we focus on whether there is a plausible mechanistic role for CRT and, if so, whether this results in acute and longer-term beneficial effects. We conclude that CRT shows promise as a potential treatment option for patients with CHD and ventricular impairment, but larger clinical outcome studies are required before definitive guidance can be issued.

© 2011 Elsevier Masson SAS. All rights reserved.

\textbf{MOTS CLÉS}
Cardiopathies congénitales

\textbf{Résumé} Les pathologies cardiaques congénitales de l’adulte représentent une nouvelle population de patients qui ne cesse de croître et qui pose des problèmes spécifiques pour leur prise en charge. La mort subite et l’installation progressive de l’insuffisance cardiaque chez ces patients jeunes représente un des challenges majeur en termes de surveillance et de

* Corresponding author. Fax: +00 33 5 57 65 68 28.
\textit{E-mail address: jean-benoit.thambo@chu-bordeaux.fr} (J.-B. Thambo).

1875-2136/$ – see front matter © 2011 Elsevier Masson SAS. All rights reserved.
Resynchronization in congenital heart disease

Stimulation cardiaque de resynchronisation ; Insuffisance cardiaque ; Asynchronisme ; Arythmies ventriculaires

Introduction

Cardiac resynchronization therapy (CRT) has been shown to be a useful therapy for adult patients with chronic left ventricular (LV) failure due to idiopathic or ischaemic dilated cardiomyopathy and electromechanical dysynchrony. It has been shown to improve exercise tolerance, heart failure symptoms, and survival [1—4]. In both European [5] and North American [6] guidelines, CRT is a class I (level of evidence A) therapy for patients with an LV ejection fraction less or equal to 35% and QRS ≥ 120 ms who remain symptomatic (New York Heart Association NYHA) functional class III—IV despite optimal medical treatment.

At the same time, the evidence is mounting that conventional dual-chamber pacing might have detrimental effects [7,8]. Several trials have shown that right ventricular (RV) apical pacing has deleterious effects on LV function, most likely due to the induction of LV dyssynchrony [7—9]. RV pacing has also been shown to have adverse effects on LV cellular structure, ventricular geometry, and systolic and diastolic function, all of which lead to an adverse haemodynamic response [7—9].

In contrast to the vast experience with biventricular stimulation gathered in adults with acquired LV dysfunction [3,10,11], the safety and efficacy of CRT in patients with congenital heart disease (CHD) and RV dysfunction has not been fully established. Evidence is limited to case reports, retrospective analyses of heterogeneous populations, and small crossover trials conducted in the immediate postoperative period [12—17]. Although preliminary results are encouraging, the applications of CRT in patients with CHD, and the mechanisms by which it might be therapeutic, remain unclear.

In this article, we review the indications and technical aspects for implantation of CRT devices in patients with CHD. We evaluate the various short- and intermediate-term results and discuss future directions of biventricular resynchronization in patients with CHD.

Is there a clinical need for cardiac resynchronization therapy (CRT) in congenital heart disease (CHD)?

CHD is the most prevalent major birth defect, and currently affects more than 1% of children [18,19]. As a result of major improvements in surgical techniques, postoperative care, and medical management in recent years, the population of adults with repaired CHD, particularly patients with complex lesions [20], is increasing. The growth of this population is linear [19] and the mortality rate, at least in the early adult years, is relatively low [21]. However, this nascent demographic phenomenon is creating major issues concerning the optimal management of adults with CHD [22].

Surgery is undoubtedly the cornerstone of treatment for the majority of patients with CHD. Good short- and midterm results are, however, tempered by later complications, including the development of ventricular dysfunction and sudden death. The prevention of ventricular impairment and ventricular arrhythmias has now become one of the most important challenges we face in the management of grown-up congenital heart (GUCH) patients. RV dysfunction is an object of growing interest, although currently, the therapeutic options remain limited. Even if surgical repair has apparently restored normal architecture, it is likely that subtle and persistent abnormalities of cardiac or extracardiac structure and function persist. Additionally, the natural history of the underlying condition and/or the development of complications may all lead to the development of heart failure and/or arrhythmias even after many years.

Cardiac electromechanical dysynchrony decreases regional loading, contractile work, myocardial blood flow, and oxygen consumption in the early-activated anterior myocardium, whereas these parameters are increased in the late-activated lateral left ventricle. Asymmetrical contraction resulting from an intraventricular conduction delay is now well identified as an independent predictor of mortality in patients with heart failure due to acquired cardiopathy. In GUCH patients, electromechanical...
dyssynchrony is becoming more frequent in asymptomatic patients, either progressively or early after surgery. A relationship between electrical and mechanical dysfunction, as well as a link between myocardial remodelling, rhythm disturbances, and electromechanical dyssynchrony, probably exists. The results from a small number of studies published thus far have been encouraging. They indicate that patients presenting with CHD have an anatomic substrate that is amenable to cardiac pacing therapy; and have also shown positive effects with both biventricular and RV pacing [12–17,23]. However, it is important to highlight that the specific treatment approach is very much dependent on the underlying condition being treated. Patients with CHD are a heterogeneous population with a variety of different lesions responsible for their symptoms, such as tetralogy of Fallot (TOF), single ventricle, and systemic right ventricle. In the next part of this manuscript, we review the current evidence for the use of CRT in each of these groups.

Right ventricular (RV) impairment in surgically corrected tetralogy of Fallot (TOF)

The majority of patients with ischaemic or dilated cardiomyopathy, LV systolic dysfunction, and asynchrony have left bundle branch block (LBBB) morphologies [3]. In this setting, CRT improves haemodynamics and bioenergetics [24]. Right bundle branch block (RBBB) is almost invariably present on the electrocardiogram after surgical repair of TOF. The prognostic importance of a wide QRS is clear, as is the high correlation between QRS duration and the risk of developing ventricular arrhythmias [25–27]. While failure of the right heart is multifactorial, caused by the combined effects of pressure and volume loads, and of myocardial lesions inflicted during and after surgery, the haemodynamic consequences of this electrical anomaly may play an important role in the long-term clinical outcomes of these patients. Sudden death and progressive heart failure, the most common causes of death in this population [26,28,29], may be promoted by the remodelling induced by mechanical dyssynchrony, which therefore may be a desirable therapeutic target [30,31].

RV dysfunction has been associated with a prominent RV mechanical delay in a porcine model that emulated some of the mechanical and electrophysiological abnormalities observed in TOF [32]. Biventricular stimulation significantly improved the function of both ventricles, measured using invasive haemodynamic studies and echocardiography. In contrast, RV stimulation from three separate sites has been found to confer no functional benefit over intrinsic conduction [33]. While this model reproduced, albeit imperfectly, the anatomical and electrophysiological abnormalities observed in patients suffering from TOF, it is noteworthy that RV dysfunction was alleviated by cardiac stimulation.

Lumens et al. have observed favourable effects with stimulation of the RV free wall in a computer model of pulmonary hypertension associated with RV dysfunction [34]. This suggests that, in the presence of pulmonary arterial hypertension, stimulation of the RV free wall can: alleviate the heavy overload imposed on that wall; equalize the load conditions and amplitudes of segmental contraction; and increase RV contractility.

Acute effects of cardiac stimulation

The immediate haemodynamic effects of RV or biventricular stimulation in adults presenting with TOF, RV dysfunction, and a wide QRS have been examined in two studies [14,33]. In the study by Dubin et al., seven patients (six suffering from TOF) who presented with isolated RV dysfunction and RBBB underwent haemodynamic investigation [14]. Transvenous pacing catheters were positioned in the right atrium and ventricle. The atrioventricular (AV) interval was programmed to 90% of the PR interval. A number of different RV pacing sites were tested, including the apex, outflow tract, and septum. Overall, sequential AV pacing improved cardiac output and RV dP/dt and decreased QRS duration when compared to atrial pacing alone and normal sinus rhythm [14]. The site that optimized QRS duration did not correlate with the one yielding optimal RV function. There was, however, a strong relationship between the degree of QRS improvement and the observed increase in cardiac output.

In our study of eight adults who presented with repaired TOF, RV and LV dP/dtmax were measured invasively during: spontaneous rhythm; RV apical stimulation; and biventricular stimulation [33]. The AV delay was programmed at 70% of spontaneous to allow complete capture of both ventricles. The mean EV ejection fraction was significantly lower than in a control population. Single RV stimulation increased RV dP/dtmax, but did not increase LV dP/dtmax, whereas biventricular stimulation increased the contractility of both ventricles. These acute studies suggest that RV pacing may be beneficial in patients with heart failure and RBBB, which is contrary to RV pacing for bradycardia in the presence of normal ventricular function. Conversely, biventricular stimulation seems preferable in presence of concomitant LV dysfunction.

Acute postoperative setting

In the acute postoperative setting, the failing ventricle has traditionally been managed by inotropic support. With most inotropic agents, contractility is enhanced at the expense of increasing myocardial oxygen consumption and energy store depletion [35]. In contrast, in patients with dilated cardiomyopathy and LBBB, CRT may improve cardiac function while modestly diminishing myocardial energy demand [36]. Following complex congenital heart surgery, both AV block and intraventricular conduction delay are not uncommon.

Initial experience with CRT in CHD has focused on the acute postoperative setting. The immediate postoperative effects of CRT were initially studied in mixed populations of patients presenting with CHD, which included patients with TOF [13,37,38]. One case report described a 6-month-old infant with TOF and atresia of the left pulmonary artery in whom acute epicardial CRT led to improved LV function and successful weaning from extracorporeal circulation [39]. In all the reports, atrial synchronized RV stimulation with optimized AV delays was performed, using temporary RV wires placed during the operation. Ventricular stimulation immediately increased systemic blood pressure, enabled a
decrease in inotropic support and volume replacement, and stabilized haemodynamic function during the first postoperative 48 hours, after which stimulation could be uneventfully discontinued.

**Long-term ventricular pacing**

Interpretation of long-term clinical results of CRT in TOF patients is problematic due to the absence of dedicated studies. The only available data are from case reports or studies of CRT in patients suffering from CHD, where statistical analyses did not distinguish TOF patients from patients with other types of CHD. The first case report describing the application of CRT in a TOF patient was in an infant who developed complete AV block and had a permanent RV pacing lead implanted at the time of surgery [40]. The patient subsequently developed left heart failure and a markedly depressed LV ejection fraction. The addition of an LV lead was followed by a clear clinical improvement and his LV ejection fraction returned to normal. As well as the positive effect of CRT in TOF, this report highlighted the importance of adapting the stimulation mode to the individual patient characteristics, and supports the use of biventricular stimulation in the presence of concomitant LV dysfunction due to RV pacing. Cecchin et al. implanted CRT devices into six patients with TOF or a variant of the disease [41], while the study by Dubin et al. included 11 such patients [14,41]. CRT appeared to provide clinical benefit in these patients. Additionally, there was a suggestion that the TOF patients derived a greater treatment benefit from CRT than patients with other congenital heart lesions, such as a systemic right ventricle.

**Summary**

Patients with surgically corrected TOF presenting with RV failure with RBBB potentially have a substrate that is suitable for treatment with cardiac pacing. Little clinical data currently exists, but acute haemodynamic studies have shown improvements with RV pacing, and the small number of patients receiving CRT devices appear to have gained clinical benefit. Further clinical studies are required before CRT can be recommended in evidence-based clinical guidelines, however, it does show promise in this group of patients.

**Single ventricle**

The term "single ventricle" encompasses a spectrum of complex congenital cardiac anomalies in which there is only one ventricle to pump blood to the pulmonary and systemic vascular beds. This group of disorders includes problems such as tricuspid valve atresia, hypoplastic left- or right-heart syndromes, mitral valve atresia, and double-inlet ventricle. The development of a number of innovative operations, including the Fontan and Norwood procedures, has resulted in dramatic improvements in outcomes. However, even after excellent early results, single-ventricle patients undergoing a Fontan operation remain at risk of progressive ventricular dysfunction, which remains the leading cause of death in this population. In Fontan patients with end-stage myocardial dysfunction, heart transplantation has traditionally been the only option to improve survival. However, the limited donor supply and the high-risk nature of transplantation demand a search for alternative forms of treatment. Although ventricular impairment in Fontan patients appears to be multifactorial, CRT has been suggested as a treatment option. In at least a proportion of patients with a single ventricle there appears to be a substrate that is potentially amenable to treatment with CRT. Significant echocardiographic ventricular dyssynchrony has been demonstrated in these patients despite a limited increase in QRS duration [42,43]. In addition, compared with controls, operated single ventricle patients have significant reductions in systolic and diastolic function as well as decreased twisting and circumferential strain. The association between ventricular dysfunction and ventricular dyssynchrony suggests that CRT may have the potential to produce improvements in cardiac function in some patients with single ventricle physiology.

**Acute postoperative setting**

Bacha et al. have investigated 26 patients (mean age 28 months) who underwent single ventricle palliation at the University of Chicago Children’s Hospital, irrespective of their electrocardiographic morphology [44]. At the time of surgery, two atrial and three ventricular temporary epicardial pacing leads were placed. The objective of CRT in patients with a single ventricle is intraventricular resynchronization through multisite pacing, rather than biventricular pacing. In this study, the ventricular leads were positioned to produce an equidistant triangle, with corners as distant as possible. Despite having a narrow QRS (93.9 ± 17.5 ms) at baseline prior to treatment, CRT was associated with a significant decrease in QRS duration (71.7 ± 10.8 ms), a significant increase in cardiac index and systolic blood pressure, and a significant decrease in ventricular dyssynchrony assessed by 3D echocardiography.

**Long-term ventricular pacing**

There have been two case reports that have described the long-term impact of CRT in patients with single ventricle physiology. In the first, an 18-year-old patient with an inoperable single ventricle, wide baseline QRS duration, and depressed ejection fraction was repeatedly hospitalized for heart failure [45]. One atrial and two ventricular leads were implanted, with one ventricular lead on the right side of the single ventricle and the other on the left side. CRT induced significant acute improvement in terms of systolic blood pressure, contractility, stroke work, and mechanical efficiency. On long-term follow-up, clinical status and ejection fraction were also significantly improved.

A second patient underwent a hemi-Fontan procedure at the age of 12 months, followed by a fenestrated Fontan procedure at the age of 5 years, with implantation of a dual-chamber epicardial pacemaker for iatrogenic complete AV block [46]. This patient was hospitalized repeatedly after the procedure because of progressive heart failure, with demonstration of impaired ventricular function, mitral regurgitation, and wide-paced QRS duration. At the age of 11 years, he underwent positioning of two supplementary epicardial ventricular leads. Compared with baseline, optimal
multisite pacing produced an almost 20% increase in cardiac output. Follow-up at 3 months showed clear clinical benefit with improvement in ejection fraction and ventricular size.

Two series have included patients with single ventricles and long-term CRT. In a multicentre study [16], seven patients with a single ventricle were included. The results in these patients were not encouraging, with no improvements in ejection fraction, and only two patients obtaining clinical improvements. In contrast, the impact of CRT was found to be much more promising in a single-centre study [41] that included 13 patients with a single ventricle. They reported improvements in terms of NYHA class and ejection fraction. The different findings in these two studies may be due to differences in baseline QRS duration and pacing site. A particular effort was made in the single-centre study [41] to optimize the pacing sites and, in particular, to obtain the maximal distance between the two ventricular pacing sites.

Summary

The role of CRT in improving outcomes in patients with a single ventricle currently remains unclear. Attempts to answer this question may have been hampered by the fact that the term "single ventricle" covers a broad spectrum of complex congenital anomalies. Potentially, these different pathologies may behave differently when CRT is applied. Selection of appropriate patients and the technical aspects of the implant procedure, such as selecting appropriate lead position, may be dependent on the particular underlying substrate. At first sight, CRT may not be an obvious solution for treating patients with ventricular impairment and a single ventricle, as they typically have a narrow QRS duration. However, echocardiographic studies have suggested that at least a proportion of patients do appear to experience mechanical dysynchrony, and some investigators have obtained promising results with CRT in this group of patients.

As highlighted, there is currently limited evidence regarding the use of CRT in this group of patients. Further clinical studies are therefore clearly necessary before CRT can be recommended in clinical guidelines for patients with a failing single left ventricle, though it may be considered in the absence of other treatment options.

Systemic right ventricle

The right ventricle is systemic in congenitally corrected and complete transposition of the great arteries. The majority of adults with complete transposition of the great arteries have had atrial switch procedures during their childhood. Progressive RV dysfunction frequently complicates atrial redirection surgery, in which the right ventricle is left connected to the systemic circulation. The right ventricle is best suited to function as a low-pressure volume pump, rather than having to generate high pressures and face high resistance, which is intrinsic to the systemic circulation. In patients with end-stage systemic RV dysfunction, heart transplantation carries a high mortality, and current advice is to delay or avoid this whenever possible. Therefore, identification of novel therapeutic strategies is of critical importance.

Failure of the systemic right ventricle may be partly related to ventricular dysynchrony. A wide QRS duration (> 120 ms) has been observed in 41% of patients with TGA after intra-atrial redirection of blood and in 37% with congenitally corrected transposition of the great arteries (cTGA) [47]. Also, Chow et al. found a high prevalence of RV (32%) and inter-ventricular (57%) dysynchrony (using tissue Doppler echocardiography) in patients with complete transposition after Mustard or Senning procedures [48]. Ventricular dysynchrony was associated with RV systolic dysfunction and impaired exercise performance. The regional differences in the timing of RV contraction and the lack of myocardial coordination may partly explain the reduced pumping function, as well as contributing to the increased prevalence of significant tricuspid regurgitation [48]. Overall, the association between decreased contractility and dysynchrony in patients with systemic RV failure provides a rationale for the use of CRT.

Acute studies in the immediate postoperative setting

Janousek et al. have assessed the acute haemodynamic impact of CRT in eight patients (aged 6–29 years) with a systemic right ventricle and RBBB (n = 2) or pacing from the left ventricle (n = 6) [17]. CRT was associated with significant decreases in QRS duration and interventricular dyssynchrony, and significant increases in contractility, ejection fraction, and cardiac output. After a median follow-up of 17.4 months, RV fractional area of change increased from 18% prior to CRT to 30%. However, no reduction in tricuspid regurgitation was noted [17].

Long-term pacing

Long-term CRT for systemic RV dysfunction was first reported in case reports with opposing results. Zartner et al. described a positive impact with CRT, in terms of exercise performance and brain natriuretic peptide in a symptomatic patient with complete transposition of the great arteries and Mustard operation [49]. In contrast, Kiesewetter et al. reported negative results with prolonged CRT in three patients with systemic RV failure (one Mustard procedure and two congenitally corrected transposition of the great arteries) [50]. This was despite an initial favourable result with CRT.

Three studies have analysed the long-term impact of CRT in patients with failing systemic right ventricles. However, they are all observational studies that only included small numbers of patients. Jauvert et al. showed that CRT was technically feasible and observed improvements in cardiac mechanical function and clinical status in seven patients who presented with a failing systemic right ventricle and ventricular dyssynchrony [51]. The largest study to date is a multicentre study that included 17 patients with systemic RV failure who received CRT [16]. These patients had a significant increase in systemic ejection fraction and a significant decrease in QRS duration; and 13 patients also had clinical improvement. In the study conducted by Cecchin et al., nine patients with a systemic right ventricle underwent CRT, but
only four patients were felt to have responded to therapy in the long term [41].

**Summary**

The mixed results from these small, non-randomized, non-controlled studies emphasize the need for further clinical research in this area. Further acute studies may be helpful to better characterize patients who show a positive acute response. Ultimately, in order to definitively answer the question of clinical outcome in this group of patients, large randomized multicentre outcome studies would be required. From a technical point of view, the coronary sinus is usually inaccessible from the systemic veins in most patients who have had the Mustard or Senning operation. They may therefore require alternative approaches to achieve CRT. In contrast, coronary sinus lead placement appears anatomically feasible in congenitally corrected transposition of the great arteries.

**Conclusions**

In patients with CHD, a relationship exists between electrical and mechanical dysfunction, as well as a link between myocardial remodelling, rhythm disturbances, and electromechanical dysynchrony. Depressed contractility and remodelling may be promoted by the presence of mechanical dysynchrony, which, therefore, may be a desirable therapeutic target. Studies of the safety and efficacy of CRT in patients with CHD are limited to case reports, retrospective analyses of heterogeneous populations, and small crossover trials conducted in the immediate post-operative period. CRT is not currently recommended in international guidelines [52]; and randomized studies are warranted before application of CRT in clinical practice in this specific subset of patients.

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

**References**


