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Cardiac resynchronization therapy in pediatric heart failure

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ABSTRACT

Heart failure is implicated in nearly 300,000 deaths annually, and is the leading cause of death or disability in adults in the United States [1,2]. Patients with heart failure often demonstrate mechanical dyssynchrony, characterized by dyskinetic ventricular contraction, regional myocardial hypokinesis, and perturbations in the natural ventricular geometry. Mechanical dyssynchrony may be associated with electrical dyssynchrony, an abnormal ventricular depolarization pattern, which is often accompanied by a bundle branch block on ECG. Such alterations in the normal contraction pattern of the left ventricle can lead to poor hemodynamics, altered ventricular function, and even changes in myocyte structure.

Cardiac resynchronization therapy, which involves the individual pacing of the right atrium as well as both ventricles to provide a more physiologic atrio-ventricular (AV) delay and a more synchronous contraction of the left and right ventricles, re-establishes a more normal contraction pattern and has been shown to be an effective treatment for heart failure due to left ventricular dysfunction in adults. In children, the role of cardiac resynchronization therapy is less well understood. Given the diverse etiologies of dilated cardiomyopathy in children as well as the individual anatomic and physiologic considerations of patients with congenital heart disease, re-establishing physiologic synchrony and improving ventricular function are considerable challenges in pediatric cardiology. This manuscript describes the more recent exploration of cardiac resynchronization therapy in the pediatric population, with emphasis on its emerging use in patients with heart failure associated with congenital heart disease, including the situation of the single ventricle.

1. Introduction

Heart failure is implicated in nearly 300,000 deaths annually, and is the leading cause of death or disability in adults in the United States [1,2]. Patients with heart failure often demonstrate mechanical dyssynchrony, characterized by dyskinetic ventricular contraction, regional myocardial hypokinesis, and perturbations in the natural ventricular geometry. Mechanical dyssynchrony may be associated with electrical dyssynchrony, which is often accompanied by a bundle branch block pattern on surface electrocardiogram. Furthermore, traditional right ventricular pacing, which activates the heart from apex to base, has been shown to induce left ventricular dyssynchrony via the loss of the normal biventricular activation sequence [3]. Such alterations in the normal contraction pattern of the left ventricle can lead to poor hemodynamics, altered ventricular function, and even changes in myocyte structure [4].

Cardiac resynchronization therapy (CRT), which involves the pacing of the right atrium as well as both ventricles to provide a more physiologic atrio-ventricular delay and more synchronous contraction of the left and right ventricles, establishes a more normal contraction pattern and has been shown to be an effective non-pharmacologic treatment for some patients with heart failure and left ventricular dysfunction. In adults, the benefits of CRT have been validated in large multi-institutional studies demonstrating a reduction in morbidity and mortality, as well as hemodynamic improvement, restoration of electrical and mechanical synchrony, and left ventricular remodeling. Clinical improvement, including improvements in NYHA functional class as well as reductions in heart failure related hospitalizations have also been demonstrated [5,6].

In adults, cardiac resynchronization therapy is currently indicated for patients with New York Heart Association functional class III to IV heart failure, an ejection fraction of <35%, a QRS duration >120 ms, with sinus rhythm, who are already on optimal medical therapy (Table 1) [7]. Even with these specific indications, the non-response rate to CRT remains high. Additionally, there are a significant number of patients who do not meet the above criteria, including those with a narrow QRS or those with early or mild heart failure, who may benefit from resynchronization. In the pediatric population, where ischemic heart disease is uncommon, the causes of heart failure range from dilated cardiomyopathy to failed palliation of congenital heart disease. Despite this variability, a body of literature is growing to support a role for CRT in some pediatric patients, including those with primary cardiomyopathies as well as those with congenital heart disease. However, as is the case for application of CRT to adults, patient selection remains a major challenge. Current areas of investigation include exploring the role of more advanced imaging modalities, including velocity vector echocardiography and functional magnetic resonance imaging as tools to more accurately identify patients

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Table 1
ACC/AHA/NASPE Guidelines for CRT in Dilated Cardiomyopathy.
From ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices.

1. New York Heart Association functional class III or IV.
2. Ejection fraction <35%.
3. QRS duration greater than or equal to 130 ms.
4. Left ventricular end diastolic diameter greater than or equal to 55 mm.

with dyssynchrony in an effort to maximize the utility of this emerging therapy.

2. Development of cardiac resynchronization therapy in adults

2.1. Early studies and pivotal trials

The first case report of cardiac resynchronization therapy was published by Cazeau et al. in 1994, describing the placement of a four-chamber system in a 54 year-old man with NYHA class IV heart failure, first-degree heart block, and left bundle branch block [8]. Acute hemodynamic evaluation of the patient demonstrated an immediate improvement in QRS duration from 200 to 160 ms, and a reduction in the pulmonary capillary wedge pressure from 36 to 26 mm Hg with biventricular pacing compared to standard A–V pacing or no pacing at all. After placement of permanent leads, re-evaluation at six weeks revealed significant clinical improvement, with reduction in peripheral edema and improvement to NYHA function class II. In all pacing modes at six weeks, the pulmonary capillary wedge pressure remained between 16 and 18 mm Hg and cardiac output ranged from 6.15 to 6.54 liters/minute, significantly improved from the acute study. The first case series of resynchronization therapy, published soon thereafter by Cazeau and colleagues in 1996, as well as those by Foster in 1995 and Blanc in 1997 also showed that multi-site pacing resulted in improvements in cardiac index and hemodynamics [9–11].

The 2001 MUSTIC trial was the first randomized, controlled study to compare the safety and efficacy of biventricular pacing versus traditional VVI pacing in patients with heart failure and intraventricular conduction delay, using functional capacity (six-minute walk test) as the primary end point [12]. Sixty-seven patients from 15 European medical centers with NYHA class III heart failure, left ventricular ejection fraction <35%, left ventricular end-diastolic diameter >60 mm, and a QRS duration at least 150 ms underwent transvenous placement of one atrial and two ventricular pacing leads. Using a single-blind, randomized crossover design, subjects received three months of VVI pacing at 40 bpm and three months of atrio-biventricular pacing. During the resynchronization period, QRS duration shortened by 25 ms, peak oxygen consumption improved by 8% ($P<0.03$), and the distance walked increased by 23% (399 +/− 100 m versus 326 +/− 134 m, $P<0.001$). There was also a two-thirds reduction in heart failure hospitalizations in the CRT group ($P<0.05$). The quality-of-life score as ascertained by the Minnesota Living with Heart Failure questionnaire, improved by 32%. Additionally, 85% of patients preferred the atrio-biventricular system to the inactive stimulation mode ($P<0.001$).

Although the findings from the MUSTIC trial were strong, the validity of the data were somewhat limited by its single-blinded, crossover design. In response to these limitations, the MIRACLE study was performed [13]. This study, published in 2002, used a randomized, double-blind design in a study of 453 subjects similar to those in the MUSTIC trial (NYHA functional class III or worse, LVEF <35%, LVEDD >55 mm, QRS >130 ms), who were randomized to a standard therapy arm, and a resynchronization arm treated with atrio-biventricular pacing. The patients in the resynchronization group showed improvement in the six-minute walk test (+39 m versus +10 m, $P=0.005$), functional class ($P<0.001$), quality-of-life score (−18 versus −9, $P=0.001$), time spent on the treadmill during exercise testing (+81 versus +19 s, $P=0.001$), and ejection fraction (+4.6% versus −0.2%, $P<0.001$). They also had a lower rate of hospitalization (8% versus 15%, $P<0.05$) or need for intravenous medications for heart failure (7% versus 15%, $P<0.05$). The MUSTIC and MIRACLE trials represent the first large, multicenter evaluations of CRT, including the first double-blinded design. Both studies clearly demonstrated improvements in hemodynamics, functional capacity, and quality of life, including a reduction in hospitalizations for moderate-to-severe heart failure in adults, and continue to serve as the foundation for ongoing research as to the role of cardiac resynchronization therapy for the treatment of congestive heart failure in both adults and children.

The impact of CRT on mortality is complex. McAlister, et al., in 2004, reviewed nine studies (3216 patients), finding that although CRT reduced all-cause mortality by 21%, it was not shown to reduce overall cardiac deaths, primarily because of an increased number of sudden cardiac deaths in the CRT population [14]. The COMPANION trial, the first large, multi-center, prospective study to evaluate cardiac resynchronization therapy with survival as a primary endpoint, evaluated 1520 adult patients with ischemic and non-ischemic cardiomyopathy, ejection fraction less than 35%, New York Heart Association class III or greater congestive heart failure, and a QRS duration >120 ms. The authors reported reduced mortality in patients receiving CRT, showing that its use reduced heart failure death or hospitalization by 34% ($P<0.002$), or 40% ($P<0.001$) if the pacemaker included a defibrillator [15]. A pacemaker reduced the risk of death from any cause by 24% ($P=0.059$), and a pacemaker–defibrillator reduced the risk by 36% ($P=0.003$). Furthermore, the CRT group had improvements in the 6 min walk test, quality of life assessment, and systolic blood pressure at three, six, and twelve months as compared to the group receiving pharmacologic therapy alone [16]. A reduction in death or unplanned hospitalization attributable to CRT alone was also demonstrated in the CARE-HF trial in 2005 [17].

2.2. Current issues

One of the great challenges to the use of CRT remains patient selection. Currently, ACC/AHA guidelines exist to select patients for cardiac resynchronization therapy that essentially recapitulate the inclusion criteria of the MIRACLE and MUSTIC trials. However, a high non-responder rate of 25–30% suggests that these criteria are not optimal [18]. Improving patient selection for CRT is critically important, given the substantial risks of performing invasive procedures on patients with advanced heart failure, as well as the high cost of CRT implantation. In a review published in JACC in 2010, Van Bommel and colleagues described several subgroups for which recent study suggests that CRT may be of benefit, including those with mild (NYHA class II) heart failure, or those with significant systolic dysfunction in the absence of a widened QRS [19]. The potential benefit of CRT in patients without a bundle branch block is critical because recent data suggests that nearly 42% of adults with heart failure have a QRS duration <120 ms [20]. The RethinQ trial, a study of 172 patients with moderate-severe heart failure and standard indications for ICD placement, included 126 patients with a QRS <120 ms. Although the study demonstrated an improvement in NYHA functional class by at least one point in more patients who received CRT than in controls (54% versus 29%, $p=0.006$), a significant change in peak oxygen consumption, quality-of-life score, or functional class in the study group, was not demonstrated. Furthermore, in comparative subgroup analysis, peak oxygen consumption improved only in those with a QRS >120 ms ($P=0.02$), leading the authors to conclude that CRT may only be of benefit in patients with a bundle branch block [21].

Also in question is the role of CRT in patients with early or mild heart failure. The recent MIRACLE-ICD trial investigated the role of CRT in patients with NYHA functional class II heart failure, and demonstrated significant improvement in left ventricular systolic volume ($p=0.01$), diastolic volume ($p=0.04$), and functional class