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Review

Cardiac resynchronization therapy in adults with congenital heart disease

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ABSTRACT

Cardiac resynchronization has become a staple in the armamentarium of heart failure management in adults. However, given the heterogeneous nature of congenital heart disease it is difficult to uniformly extrapolate all adults with congenital heart disease whose ejection fraction is ≤35% as appropriate CRT candidates. Rather the practitioner managing a heart failure adult with congenital heart disease should think of the defect as being in one of four distinct categories: (1) failing systemic left ventricle, (2) failing systemic right ventricle, (3) failing pulmonary right ventricle, or (4) a failing single ventricle. The Pediatric and Congenital Electrophysiology Society in conjunction with the Heart Rhythm Society recently published consensus guidelines for Arrhythmia Management in the Adult with Congenital Heart Disease. Within that document, a subsection exists to provide some guidelines on CRT in this challenging population. This review will highlight the largely retrospective studies that have evaluated adults with CHD who received CRT and understand why some patients respond and others do not.

1. Introduction

Heart failure occurs in 2% of adults and is a significant cause of morbidity and mortality, and a major burden in global health care dollars [1,2]. Cardiac resynchronization therapy (CRT) is a viable option for adults with chronic left ventricular (LV) failure secondary to idiopathic or ischemic dilated cardiomyopathy despite optimal medical management. CRT improves LV function by correcting the electromechanical dyssynchrony (EMD) and introduces a more synchronous contraction pattern. As a result in selected heart failure patients, CRT improves heart failure symptoms, reduces New York Association (NYHA) functional class, improves exercise tolerance, and reduces all-cause mortality. Given the overwhelming data in large scale randomized adult heart failure trials in both Europe and North America, the current adult heart failure guidelines recommend CRT for patients with NYHA class III–IV, ejection fraction ≤35% and a QRS duration >120 msec [3–5]. However, extrapolating adult heart failure recommendations to adults with congenital heart disease (ACHD) is fraught with many inaccuracies. ACHD patients may have systolic or diastolic myocardial dysfunction secondary to a dysfunctional single ventricle, systemic LV, systemic right ventricle (RV), or have overt heart failure related to a failing pulmonary RV. Furthermore adult non-CHD heart failure patients tend to have electrical dyssynchrony with a left bundle branch block (LBBB) pattern. ACHD heart failure patients tend to have right bundle branch block (RBBB) and while they may exhibit electrical dyssynchrony, determining who has concomitant mechanical dyssynchrony may be difficult.

2. Ventricular Dyssynchrony

Electrical dyssynchrony results from abnormal electrical activation and is a major cause of mechanical dyssynchrony. This may relate to chronic RV apical pacing in congenital or acquired post-surgical heart block. In LBBB, the electrical activation is initiated within the interventricular septum and slowly propagates via intramyocardial conduction to the LV free wall. In hearts with right bundle branch block (RBBB), the free wall of the RV contracts late and the lateral LV wall contracts early against a quiescent septum. However, differences in the RV and LV geometries may account for less pronounced hemodynamic perturbations compared to LBBB. This may explain why not all patients with RBBB respond favorably to CRT. Optimizing cardiac pump function with CRT generally relates to an understanding of the electrical ventricular dyssynchrony and its relation to mechanical dyssynchrony. Mechanical dyssynchrony may result from abnormal myocardial loading conditions and contractile disparity [6–9]. A prolonged QRS duration is consistent with electrical dyssynchrony but does not reliably confer mechanical dyssynchrony, nor does it absolutely predict which patients will respond favorably to CRT. EMD relates to discordance in the time of contraction and relaxation between myocardial segments. Early electrical activation and mechanical contraction causes initial stretch of late activated segments and by the time those late segments contract, the

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early myocardial segments have begun to relax. Local myocardial work is decreased in the early contracting sites with low local preload, but increased in the late contracting segments that have augmented preload that is enhanced by the preceding stretch [10]. These volumetric regional abnormalities may lead to asymmetric hypertrophy with decreased local wall thickness in the early contracting sites and myocardial hypertrophy in the late contracting sites [10]. A number of cellular changes occur in the presence of mechanical dyssynchrony that may further compound ventricular dysfunction. Decreased calcium cycling impairs excitation–contraction coupling [11]. Beta-adrenergic stimulation response to stress is down-regulated [12]. The late activated myocardial segments have decreased myocardial conduction velocities secondary to Connexin 43 down-regulation [13]. This dyssynchrony, and inefficient myocardial work, are theoretically amenable to CRT. CRT electrically pre-excites the late contracting myocardial segments and restores normal mechanical contraction and augments contraction efficiency [14].

In contrast to the vast number of large multicenter CRT trials in adults with heart failure, the safety and efficacy of multisite pacing in patients with CHD has been limited [5,15,16]. Large-scale prospective randomized trials in the ACHD population are absent. Efficacy of CRT in the ACHD patient may vary with the anatomic substrate, degree of AV valve regurgitation, type of bundle branch block, myocardial scarring, and degree of electrical anisotropy [17–19]. As the indications for CRT shift in the adult HF population, should similar considerations exist in ACHD patients towards device implantation in those with milder forms of heart failure related symptoms?

2.1. Systemic LV

The group of patients with systemic LV failure and EMD is similar to non-ACHD adult CRT patients. Congenital or post-operative AV block with chronic RV pacing accounts for 65% of CRT indications in ACHD subjects [17–20]. Favorable outcomes have been reported in this subgroup, and especially among the cohort with chronic RV apical pacing.

2.2. Systemic RV

Systemic RV failure frequently occurs in patients with D-transposition of the great vessels (TGA) with intra-atrial baffle procedures or in patients with congenitally corrected transposition (L-TGA). Both groups have an unfavorable long-term natural history. Patients late after D-TGA and intra-atrial baffle procedures (Mustard or Senning) are at risk of sinus node dysfunction and atrial arrhythmias. Patients with L-TGA are at risk of AV block secondary to the abnormal course of conduction tissue as it passes anteriorly along the LV free wall in the vicinity of the pulmonary valve. Additionally, the tricuspid valve is exposed to systemic arterial pressure further contributing to ongoing morbidity and mortality [21]. Standard CRT criteria apply to less than 5% of ACHD patients with a systemic RV. In fact, increased efficacy of CRT has been achieved when a stricter definition of interventricular and intra-ventricular dyssynchrony is employed. In small case series of patients with systemic right ventricles, CRT has been shown to increase RV ejection fraction, decrease QRS shortening, increase peak VO_2, and reduce NYHA classification [17,18,22,23]. However, tricuspid valve regurgitation does not appear to be significantly influenced by CRT. [23] Recently, there has been concern over the possibility of CRT resulting in sub-pulmonary left ventricular dysfunction in patients with a failing systemic right ventricle [24]. A follow-up registry is critical to help answer some of these questions in ACHD patients with a systemic RV who underwent biventricular pacing.

2.3. Pulmonary RV

Patients who have undergone tetralogy of Fallot (TOF) repair often present with RBBB. However, not all RBBB abnormalities are similar. RBBB may be central, proximal, or distal and the resulting degree of dyssynchrony further compounds an already heterogeneous population. What is the contribution to the degree of dyssynchrony based on a VSD? Ventriculotomy? Infundibulotomy? Pulmonary hypertension? Pulmonary insufficiency? All of these features may localize a region of dyssynchrony and intraventricular dyssynchrony that may be more relevant than interventricular dyssynchrony. Myocardial scarring over time can further impinge on the conduction of the RV and LV [25,26]. It is well known that TOF adults have progressive RV systolic and/or diastolic dysfunction leading to increased heart failure. However, left ventricular dysfunction may act as a concomitant source of clinical heart failure [27]. It has been estimated that nearly 20% of adults with repaired TOF will have mild LV systolic dysfunction and 5–10% will have moderate-plus LV dysfunction [25,26]. Additionally, LV systolic and diastolic dysfunctions may be a harbinger of ventricular arrhythmias and sudden cardiac death [28]. In a recently published paper, adult patients with repaired TOF and LV systolic dysfunction demonstrated a significant mid-term response to CRT; LVEF increased from 24% to 37%, even in the presence of RV conduction delay [29].

2.4. Technical Considerations

Technological advancements in leads and sub-selected sheaths have evolved and facilitated delivery of pacing leads to even more difficult to reach chambers of interest. Prior to CRT implantation, a detailed assessment of the anatomy is critical. Prior surgical procedures, interventional cardiac angiograms should be reviewed. Understanding potential vascular routes to the desired chamber should be done prior to the start of the procedure. Cardiac anatomic boundaries may exist that preclude a 100% endocardial approach, such as certain Fontan procedures and prosthetic AV valves. In addition, atrial baffles may be stenotic and require stent placement before endocardial lead deployment. Residual intracardiac shunt and baffle leaks combined with the thrombogenic milieu of an endocardial lead increase the risk of stroke [30]. A subset of patients with congenital heart disease may have a left subclavian vein that only drains to the coronary sinus and careful preoperative planning in those instances should take such a factor into consideration. Depending on the surgery performed, the coronary sinus may in fact drain into either the systemic atrium or pulmonary neo-atrium [31]. A hybrid (combined epicardial and endocardial) approach should be considered in patients whose coronary sinus cannot be accessed from a traditional vascular approach.

3. ACHD Candidates for CRT

A recent combined pediatric and adult task force from the Pediatric and Congenital Electrophysiology Society (PACES) and Heart Rhythm Society (HRS) has published arrhythmia guidelines for ACHD patients. A section of the document addressed recommendations of CRT for ACHD patients. The following summarizes the current 2014 CRT recommendations (published Heart Rhythm Society website: http://www.hrsonline.org/Practice-Guidance/Clinical-Guidelines-Documents/2014-Recognition-and-Management-of-Arrhythmias-in-Adult-Congenital-Heart-Disease)

Class I (indicated)

A.

- Systemic LV ejection fraction ≤35%
- Sinus rhythm (LBBB with a QRS complex ≥150 ms) (spontaneous or paced)
- NYHA class II to IV (ambulatory) symptoms

Class IIA (can be useful)

A.

- Systemic LV EF ≤35%
- Sinus rhythm (LBBB with a QRS complex 120–149 ms) (spontaneous or paced)
- NYHA class II to IV (ambulatory) symptoms