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Cardiac resynchronization therapy for adult congenital heart disease patients with a systemic right ventricle: analysis of feasibility and review of early experience

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Aims Patients with a systemic right ventricle (RV) frequently develop heart failure and may benefit from cardiac resynchronization therapy (CRT). We aimed to assess the proportion of unselected patients with a systemic RV eligible for CRT and to review available data on the effect of CRT in congenital heart disease patients.

Methods and results Adhering to criteria derived from landmark CRT trials, we determined the eligibility of patients with a systemic RV for CRT. Seventy-five transposition of the great arteries (TGA) patients (age 29.5 $\pm$ 10.2 years) and 49 patients with congenitally corrected (cc) TGA (age 36.2 $\pm$ 12.8 years) were studied. Full criteria for CRT were met in 4.0% of the TGA patients and 4.1% of the ccTGA patients. Including New York Heart Association class 2 patients, 9.3% of TGA and 6.1% of ccTGA patients were eligible for CRT.

Conclusion Four to 9% of unselected patients with a systemic RV appear to be potential candidates for CRT. Although large clinical studies are currently lacking, available data consistently demonstrate that CRT improves haemodynamics in congenital heart disease patients and warrants further investigation.

Introduction

Ventricular dysfunction is common in adult congenital heart disease (ACHD) patients with a systemic right ventricle (RV) and is, in part, related to electromechanical dyssynchrony.[1–3] Over 25% of such individuals ultimately progress to symptomatic heart failure, which is occasionally refractory to drug therapy and associated with substantial morbidity and mortality.[3] Therefore, identification of novel therapeutic strategies in this cohort is of critical importance. Given that a large number of patients with a systemic RV will require conventional pacemaker therapy[4] which in the presence of ventricular dysfunction and conduction disease may further compromise cardiac performance,[5,6] devices capable of combining conventional pacing with modern functions geared towards ameliorating ventricular function seem to offer an obvious advantage.

Cardiac resynchronization therapy (CRT) is rapidly emerging as an effective treatment option for patients, on optimal medical treatment, with acquired unremitting heart failure and electrocardiographic stigmata of ventricular dyssynchrony.[7,8] Although small studies conducted in selected ACHD patients suggest that CRT may also be beneficial,[1,9] the proportion of unselected patients with a systemic RV that are potentially eligible for CRT is unclear.

In this study, we sought to assess what proportion of unselected patients with a systemic RV are potentially eligible for CRT according to the inclusion criteria used in landmark CRT trials. In addition, we review the currently available data on the effect of CRT in ACHD patients.

Methods

Proportion of patients with systemic RV appropriate for CRT

This was a retrospective study conducted at a tertiary referral centre caring for adult patients with congenital heart disease. From a computerized database, we identified all patients with either transposition of the great arteries (TGA) after intra-atrial redirection of blood (Mustard or Senning type atrial switch

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operations) or congenitally corrected (cc) TGA who were under active follow-up at our institution. Adhering to the criteria derived from landmark CRT trials [New York Heart Association (NYHA) class $\geq$3, sinus rhythm, ventricular dilatation, ventricular dysfunction, and prolonged QRS duration; *Table 1*), we determined the potential eligibility of patients for CRT. Echocardiographic recordings were reviewed and systemic systolic ventricular function and dimensions were classified semiquantitatively as previously described.[10] Systolic ventricular function was graded as normal, mildly impaired, moderately impaired, or severely impaired. Cardiomegaly was defined as a cardiothoracic ratio $\geq$0.5 on postero-anterior chest radiographs. The most recent ECG was evaluated for underlying cardiac rhythm, QRS duration, and bundle branch block pattern. Patients' symptomatic status was scored according to the NYHA classification. Full criteria for CRT were defined as NYHA class $\geq$3, at least moderate systolic ventricular dysfunction, at least moderate ventricular dilatation on echocardiography or cardiomegaly on chest radiographs, and a QRS duration $\geq$120 ms (QRS duration $\geq$200 ms with conventional pacing). Additionally, a subgroup of patients had undergone cardiopulmonary treadmill exercise testing with respiratory gas analysis (Amis 2000, Innovision, Odense, Denmark) as previously described.[11] These patients were compared with age-matched healthy controls ($n = 10$ for each diagnosis) within our department.

Standard methods of descriptive statistics were employed. All values are presented as mean $\pm$ standard deviation (SD). Comparisons between groups were made using Student's *t*-test, Mann–Whitney *U* test or χ^2 test as appropriate.

Patients with TGA after intra-atrial redirection of blood

Seventy-five surgically palliated TGA patients (42 males) with a mean age of 29.5 years (SD: 10.2 years) were included. The majority of patients was in sinus rhythm (72.1%); 14.7% had a conventional pacemaker (AAI, $n = 3$; VVI, $n = 4$; DDD, $n = 4$).

Electrocardiographic evidence of conduction delay (QRS duration $\geq$120 ms) was found in 40.7% of patients without a pacemaker (22.2% with a QRS duration $\geq$130 ms and 7.4% with a QRS duration $\geq$150 ms, respectively). None of these patients had typical left bundle branch block, whereas 16.7% of TGA patients showed right bundle branch block. A QRS duration of $\geq$200 ms was recorded in 30% of patients fitted with a conventional pacemaker.

Echocardiographic data revealed that systemic ventricular function was at least moderately reduced in 30.6% of TGA patients, whereas ventricular dilatation ($\geq$moderate) was present in 50.9% of patients. In addition, radiographic evidence of cardiomegaly was present in 69.6% of patients.

The majority of patients reported themselves as being asymptomatic (52.9% in NYHA class 1), 33.8% of patients were in NYHA class 2, and only 13.2% had NYHA class 3 symptoms. However, in those patients who underwent formal exercise testing with metabolic monitoring ($n = 37$), peak oxygen consumption was significantly lower when compared with healthy age-matched controls (TGA patients 25.5 ± 6.5 vs. 44.5 ± 7.4 mL/kg/min in age-matched controls, $P < 0.0001$). This result remained unchanged even if only asymptomatic TGA patients were considered (27.4 ± 6.7 vs. 44.5 ± 7.4 mL/kg/min, $P < 0.0001$). In addition, a peak oxygen consumption $<$18 mL/kg/min (as used in the PATH-CHF II trial as an inclusion criteria in a much older population) was found in 13.5% of our TGA patients.

Patients with ccTGA

Forty-nine ccTGA patients (22 males) were studied. The mean age was 36.2 years (SD: 12.7 years). Similar to surgically palliated TGA patients, the majority of ccTGA patients was in sinus rhythm (63.6%); 24.5% of ccTGA patients had a conventional pacemaker (DDD, $n = 7$; VVI, $n = 5$) *in situ*.

Electrocardiographic evidence of conduction delay (QRS duration $\geq$120 ms) was found in 37.5% (21.8% with a QRS duration $\geq$130 ms and 9.4% with a QRS duration $\geq$150 ms, respectively) of patients without an implanted pacemaker. Typical left bundle branch block pattern was found in 15.6% of them. In addition, 25% of patients with a pre-existing pacemaker had QRS durations $\geq$200 ms.

Systemic ventricular function was at least moderately reduced on echocardiography in 33.3% of ccTGA patients and ventricular dilatation ($\geq$moderate) was present in 28.1% of patients. Cardiomegaly on chest radiographs was found in 52.3% of ccTGA patients.

The majority of ccTGA patients was symptomatic (58.1% of patients were in NYHA class $\geq$2, with 18.6% in NYHA class 3). Consistent with the surgically palliated TGA patients, peak oxygen consumption was lower in ccTGA ($n = 33$) when compared with age-matched controls (21.4 ± 9.9 vs. 39.2 ± 9.2 mL/kg/min, $p < 0.0001$). This result remained unchanged when only asymptomatic ccTGA patients were considered (26.0 ± 7.9 vs. 39.2 ± 9.2 mL/kg/min, $P = 0.005$). A peak oxygen consumption $<$18 mL/kg/min was evident in 33% of ccTGA patients.

Proportion of patients with a systemic RV potentially eligible for CRT

Using criteria derived from landmark CRT trials (*Table 1*), we found that 4.0% of surgically palliated TGA patients and 4.1% of ccTGA patients were potentially eligible for CRT. Including patients in

Table 1 Inclusion criteria employed in the randomised clinical trials evaluating the effect of CRT in chronic heart failure

	Rhythm	NYHA	Ventric. dilatation	Ventric. dysfunction	QRS duration	*n*
InSync[16]	Sinus	3/4	Yes	Yes	>150	103
MUSTIC[7]	Sinus	3	Yes	Yes	>150	58
MUSTIC AF[17]	AF	3	Yes	Yes	>200[a]	43
MIRACLE[8]	Sinus	3/4	Yes	Yes	>130	453
CONTAK CD[18]	Sinus	2/3/4	No	Yes	>120	581
Care-HF[33]	Sinus	3/4	Yes	Yes	>120	800
PATH-CHF[19]	Sinus	3/4	No	No	>120	42
PATH-CHF II[29]	Sinus	2/3/4[b]	No	Yes	>120	101
COMPANION[20]	Sinus	3/4	Yes	Yes	>120	1520

AF, atrial fibrillation; ventric. dilatation, ventricular dilatation (>60 mm left ventricular end-diastolic dimension in the majority of studies); ventric. dysfunction, systolic ventricular dysfunction (left ventricular ejection fraction <35% in most studies).
[a]QRS duration > 200 ms in patients with an implanted conventional pacemaker.
[b]Only patients with a peak oxygen consumption below 18 mL/kg/min were enrolled in PATH-CHF II.

NYHA class 2, and without considering ventricular dilatation (i.e. criteria similar to CONTAK CD or PATH-CHF II), 9.3% of surgically palliated TGA and 6.1% of ccTGA patients fulfilled the criteria used for enrolment in the aforementioned trials.

Discussion

In an unselected cohort of ACHD patients with a systemic RV, we demonstrate that abnormalities (systolic ventricular dysfunction, ventricular dilatation, and QRS prolongation) employed as inclusion criteria in landmark CRT trails are commonly present, with 4–9% of our study population meeting these inclusion criteria.

Rationale and early experience of CRT in ACHD patients

Adult congenital heart disease patients represent an expanding population that is growing at a rate of 5% per annum.[12] Substantial evidence has highlighted that ACHD shares similar pathophysiological characteristics with the syndrome of chronic heart failure, namely exercise intolerance,[13] neurohormonal activation, immune dysregulation,[10,14] electromechanical aberrations,[2] and by definition structural abnormalities of the heart.[15] Therefore, extension of proven heart failure therapies into the field of ACHD is a logical next step. Patients with a systemic RV are particularly prone to ventricular dysfunction, which commonly progresses to overt symptomatic heart failure[3] and may be partly related to ventricular dyssynchrony. Such individuals may derive benefits from CRT, which are comparable with those demonstrated in patients with ischaemic or dilated cardiomyopathy.[7,8,16–20]

Cardiac resynchronization therapy attempts to improve inter- and intra-ventricular electromechanical co-ordination, hence its effects are critically dependent on the presence of baseline ventricular dyssynchrony. Several studies using echocardiography and ventricular cineangiography have demonstrated dyssynchronous ventricular contractions in patients with a systemic RV,[1,2] tetralogy of Fallot[21,22] and Fontan palliation[23] (*Table 2*). Subsequently, Janousek *et al.*[9] demonstrated that CRT acutely augmented arterial blood pressure in 20 children with various lesions immediately after cardiac surgery. In 29 patients with assorted lesions and prolonged QRS durations, Zimmerman *et al.*[24] demonstrated similar benefits, with CRT facilitating weaning from cardiopulmonary bypass. In seven patients with RV dysfunction and right bundle branch block, Dubin *et al.*[25] reported that resynchronization therapy acutely improved cardiac index and RV contractility. A subsequent retrospective study by Strieper *et al.*[26] with a median follow-up period of 19 months showed that CRT shortened QRS durations and improved clinical status and ejection fraction in five paediatric patients. In a recent prospective analysis, Janousek *et al.*[1] reported that CRT improved electromechanical dyssynchrony and augmented haemodynamics in eight patients with a systemic RV. These effects were sustained over a median follow-up period of 17 months. Recent studies have also suggested that CRT may be a particularly useful adjunct in the management of selected ACHD patients early after cardiac surgery. Using three-dimensional echocardiography, Bacha *et al.*[27] prospectively demonstrated that CRT improved ventricular co-ordination and cardiac performance in 26 paediatric patients early after single-ventricle palliation.

Proportion of patients with a systemic RV appropriate for CRT

Although CRT has been shown to confer acute benefits in a small number of selected ACHD patients, it is unclear what proportion of unselected patients with a systemic RV potentially stand to benefit from this emerging technology. In this analysis of 124 consecutive adult patients with a systemic RV, we found that 4–9% fulfiled inclusion criteria adopted in landmark CRT trials conducted in non-congenital cohorts. Although such criteria are not validated in this cohort, our figures are concordant with reports in patients with acquired dilated or ischaemic cardiomyopathy, where $\sim$10% was shown to be appropriate for CRT.[28]

Electrical dyssynchrony was common in our cohort, even in those patients who did not meet all criteria for CRT. A QRS duration $>$120 ms was evident in 41 and 37% of surgically palliated TGA and ccTGA patients, respectively, and is potentially associated with mechanical dyssynchrony. This is consistent with the ample data demonstrating that ventricular dyssynchrony is present in a variety of ACHD patients and has a negative impact on ventricular function.[1,2,21–23] Additionally, early evidence suggests that the haemodynamic benefits seen during CRT correlate with improvements in baseline dyssynchrony in patients with a systemic RV.[1]

Our results also indicate that many patients with a systemic RV are symptomatic, but self-reporting of exercise intolerance appears to underestimate the true degree of exercise limitation. In the present study, systemic RV patients (even allegedly asymptomatic subjects) had markedly lower peak oxygen consumptions than age-matched healthy controls. Furthermore, 13% of surgically palliated and 33% of ccTGA patients had objective exercise limitation of a comparable severity (peak oxygen consumption $\leq$18 mL/kg/min) with that employed to recruit much older patients into the PATH-CHF II trial.[29] This finding illustrates the severity of exercise intolerance in ACHD and may have implications for planning prospective studies on CRT in this population.

Coronary venous anatomy in patients with sytemic RV

Although patients with a systemic RV may have indications for CRT, their coronary venous anatomy may not be amenable to such an intervention. Although both surgically palliated TGA and ccTGA patients have a morphologic systemic RV, their coronary venous anatomy differs. The coronary sinus drains into the systemic ('right') atrium in ccTGA hearts.[30] In contrast, after surgical intra-atrial redirection of blood, the coronary sinus may drain either into the systemic or into the pulmonary neo-atrium, depending on the placement of the intra-atrial baffle. It has been reported that following atrial redirection, the coronary sinus is accessible from the systemic atrium in $\sim$50% of cases.[31,32] The coronary sinus is ontogenetically part of and located on the morphologic left atrium. Hence, the coronary sinus is situated adjacent to the RV in ccTGA patients, as opposed to the left ventricle in surgically palliated TGA hearts. Therefore, in ccTGA, the coronary sinus and its tributaries drain blood predominantly from the systemic (right morphologic) ventricle, whereas in surgically palliated TGA, they are predominately connected to the subpulmonary (left

Table 2 Studies evaluating the effect of cardiac resynchronization in patients with congenital heart disease

Study	Population studied	Patient no., age range	Outcome
Acute haemodynamic studies early after cardiac surgery			
Bacha *et al.*[27]	Single-ventricle anatomy	$n = 26$, 7 days–11 years	Improved cardiac index and synchrony of ventricular contraction
Zimmerman *et al.*[24]	Single- and biventricular	$n = 29$, 1 week–17 years	Improved cardiac index, systolic blood pressure, and shortened QRS duration
Janousek *et al.*[9]	Single- and biventricular	$n = 20$, 3.4 months–14 years	Improved systolic blood pressure and shortened QRS duration
Acute haemodynamic studies during cardiac catheterization			
Dubin *et al.*[25]	Right ventricular failure and right bundle-brunch block	$n = 7$, 1.7–53 years	Improved cardiac index, right ventricular contractility, and shortened QRS duration
Prospective clinical studies			
Janousek *et al.*[1]	Systemic RV	$n = 8$, 7–29 years	Improved systemic right ventricular ejection fraction, augmented interventricular asynchrony, and shortened QRS duration
Retrospective studies			
Strieper *et al.*[26]	Biventricular anatomy referred for transplantation	$n = 7$, 2.3–28 years	Four patients had a pre-existing conventional pacemaker. Ejection fraction, ventricular dimensions, and clinical status improved in five patients. One patient died during follow-up
Case reports			
Blom *et al.*[34]	Post-VSD closure and mitral valve replacement	6 years	Intraventricular asynchrony and clinical status improved
Roofthooft *et al.*[35]	VSD, aortic valve disease, and hypoplastic aortic arch	2 months	Upgrade from DDD to CRT. Clinical condition improved, QRS duration decreased, ejection fraction improved, and the degree of mitral regurgitation declined
Rodriguez-Cruz *et al.*[36]	Congenitally corrected TGA, pulmonary atresia, and VSD	22 years	Clinical condition, exercise capacity, arterial blood pressure, end-diastolic pressure, and left ventricular contractility improved

VSD, ventricular septal defect.

morphologic) ventricle. As a consequence, current lead placement strategies for CRT that aim to position electrodes in the lateral or infero-lateral (postero-lateral) veins overlying the systemic ventricular wall are not applicable in TGA hearts after atrial redirection of blood. Coronary sinus lead placement appears anatomically feasible in ccTGA patients, but because of variable venous anatomy, we would currently advocate the use of elective cardiac venography to assist lead implantation in these patients. In contrast, surgically palliated TGA patients will require surgical electrode placement for CRT.

Clinical implications

The results of the current study are of clinical importance as patients with a systemic RV frequently develop ventricular dysfunction,[3] require conventional pacemaker therapy,[4] and have objective exercise limitation and electrical dyssynchrony. Cardiac resynchronization may have the potential to benefit a large number of ACHD patients with varying lesions. However, these patients will pose additional challenges to CRT because of their heterogeneous anatomy and physiology.

Limitations of the current study

In the current study, we utilized criteria employed in landmark CRT trials conducted in non-congenital cohorts which have yet to be validated in ACHD patients. In contrast to patients enrolled into landmark CRT trials, the majority of our patients had conduction abnormalities other than left bundle branch block, reflecting the pivotal role of the RV in these cohorts. It remains to be elucidated whether the impact of right bundle branch block on systemic ventricular function and parameters of mechanical asynchrony are comparable with the effect of left bundle branch block present in patients with ischaemic or dilated cardiomyopathy. In addition, the current study was not designed to assess the

presence of mechanical asynchrony and its relationship to markers of electrical asynchrony in our population. Similar to patients with acquired heart disease, conduction delay on ECG may not reflect underlying mechanical asynchrony in individual patients with a systemic RV. Further studies are required to evaluate the relationship between ECG-related parameters and mechanical asynchrony in this population.

Conclusion

Our study demonstrates that 4–9% of unselected patients with a systemic RV are potentially eligible for CRT. Early experience suggests that CRT improves acute haemodynamics in patients with ACHD. Additional studies are clearly required to establish indications and timing for CRT as well as its acute and long-term effects on ventricular function and outcome in a variety of patients with ACHD.

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