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Cardiac resynchronization therapy for the failing systemic right ventricle: A systematic review

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ABSTRACT

Patients with a systemic right ventricle (SRV) are at high risk for development of heart failure early in life. An SRV is encountered in patients with congenitally corrected transposition of the great arteries (CCTGA) or dextro-transposition of the great arteries (DTGA) with previous atrial switch repair (Mustard or Senning procedure). Progressive heart failure is one of the leading cause of mortality in these patients. Therefore, cardiac resynchronization therapy (CRT) has gained increasing momentum for use in this challenging congenital heart disease (CHD) population. However, current guidelines differ in recommendations for CRT in patients with an SRV as evidence supporting CRT has thus far only been described in case reports and retrospectively in relatively small study populations. In fact, the European Society of Cardiology Guideline for the management of grown-up congenital heart disease consider CRT to be 'experimental' in this population. This systematic review critically summarizes current literature on CRT in SRV patients and provides future perspectives for further research in this challenging and growing CHD population.

1. Introduction

Cardiac resynchronization therapy (CRT) is an established therapy for patients with acquired heart disease who develop heart failure with inter- and intraventricular dyssynchrony. European and North-American guidelines provide specific indications for CRT in this population, however these criteria are not directly applicable to patients with congenital heart disease (CHD) [1,2]. Advances in medical therapy have resulted in an ever-increasing population of grown-ups with congenital heart disease (GUCH) in whom sudden cardiac death and progressive heart failure are predominant causes of mortality [3–6]. This especially true for patients with CHD and a systemic right ventricle (SRV).

SRV is commonly encountered in the form of congenitally corrected transposition of the great arteries (CCTGA) or dextro-transposition of the great arteries (DTGA) with previous atrial switch repair (Mustard or Senning operation) [7–10]. Symptomatic heart failure frequently occurs in these patients. By the age of 45, up to 65% of the patients with an SRV are afflicted with symptomatic heart failure [10,11]. Nevertheless, the pathophysiological mechanisms, and more importantly the interactions between these mechanisms underlying SRV failure are still incompletely understood. CRT has gained increasing momentum for use in SRV patients. However, current guidelines differ in recommendations for CRT in patients with an SRV as evidence supporting CRT has thus far only been described in case reports and retrospectively in relatively small study populations [12]. In fact, the European Society of Cardiology Guideline for the management of grown-up congenital heart disease considers CRT to be 'experimental' in the SRV population [13]. On the other hand, the more recent Pediatric and Congenital Electrophysiology Society and the Heart Rhythm Society (PACES/HRS) international guidelines suggest that CRT may be useful in SRV patients with reduced ejection fraction (≤35%), New York Heart Association (NYHA) function class ≥ II and QRS duration >150 ms with a complete right bundle branch block morphology (spontaneous or paced) [14].

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This systematic review critically summarizes the current literature on CRT in SRV patients and provides future perspectives for further research in this challenging and growing CHD population.

2. Methods

This systematic review was conducted according to Cochrane collaboration handbook and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15].

2.1. Search strategy

Embase.com (from 1974 to present), Medline ALL via Ovid (from 1946 to present), Cochrane Central Register of Trials (from 1992 to present) and Web of Science Core Collection (from 1900 to present) were searched from inception until 7 May 2020 (date last searched), by a medical information specialist (W.M. Bramer). The search combined keywords for cardiac resynchronization therapy or biventricular pacing with terms for congenital heart disease (Supplementary Material).

2.2. Selection criteria

Studies reporting on the outcome of CRT in patients with an SRV were included. Studies were excluded if the underlying heart disease was not reported. Studies investigating the outcome of biventricular pacing in the acute post-operative setting, case (series) reports (defined as ≤3 patients), abstracts, editorials, reviews and studies written in languages other than English were excluded from analysis. Patients with univentricular hearts were also excluded. Finally, we excluded all studies for which the full text could not be retrieved. Extracted clinical variables from all included studies are summarized in Table 1.

2.3. Data extraction and appraisal

Two researchers (R.K. Kharbanda & J.P. Moore) independently reviewed the titles and abstracts of all retrieved articles. All identified potentially relevant articles were screened for adherence to the inclusion and exclusion criteria after which the data was collected in Microsoft Access 2010. When duplicate reports were suspected, the most recent publication was included. Data appraisal was not performed, as literature on outcomes of CRT in patients with an SRV is scarce.

3. Results

The search resulted in 949 articles; after screening titles and abstract, 46 articles were considered for full-text screening. As demonstrated in Fig. 1, this resulted in 14 studies reporting the outcomes of CRT in SRV patients. All studies were retrospective in nature and the key findings are summarized in Table 1.

3.1. Single center studies

The first study to report outcomes of CRT in CHD patients included solely patients with an SRV [16]. The acute- and mid-term effects of CRT were evaluated for 8 patients (median age 13 years [7–29]). Three patients received a purely epicardial CRT-system, 4 patients received a mixed-CRT system and purely transvenous lead system was implanted in only 1 patient. After a median follow-up duration of 17.4 months [7.7–19.7], significant decrease in QRS duration and improvement in SRV function assessed by radionuclide ventriculography was observed. Tricuspid valve regurgitation, however, was not significantly reduced by CRT (mean grade prior 2.1 ± 1 vs. mean grade post 1.6 ± 1.4). This proof of concept study showed that CRT could be promising in "preventing" progressive SRV failure. The study was mainly limited by a low number of patients with none affected by severe heart failure.

Subsequently, several smaller studies demonstrated conflicting results on efficacy of CRT in SRV patients (Table 1). One such study was performed by Cecchin et al. who examined both echocardiographic and clinical response in 60 CHD patients receiving CRT [17]. The authors identified SRV non-responders as <10% increase in RV ejection fraction as compared to baseline. Subgroup analyses of 9 SRV patients (27 years [0.5–43]) with a median follow-up period of only 8 months, showed acute improvement in 5 patients (55.6%). Despite a favorable acute response in the majority of the patients, a responder rate of only 25% was reported over long-term follow-up. Another study from Jauvert et al. reviewed 7 SRV patients (24.6 years [15–50]) in order to assess echocardiographic and clinical effects of CRT in the presence of TGA [18]. All patients were in NYHA functional class III with a failing SRV and interventricular dyssynchrony of whom 5 patients received a mixed CRT-system. After a mean follow-up time of 19.4 ± 8.1 months, mean NYHA class decreased from 3 to 1.6, Vo2 max increased from 13.8 ± 2.5 ml/kg/min to 22.8 ± 6.7 ml/kg/min and QRS duration decreased from 160 ± 31 ms to 120 ± 28 ms. Importantly, several patients had single chamber ventricular pacing for sinus node dysfunction at baseline.

Yeo et al. reported on 7 CCTGA patients undergoing CRT (46 ± 10 years) and included two comparison groups of chronic subpulmonary LV pacing and un-paced patients [19]. There was no clear definition used to determine CRT response and data were not reported for each patient separately. The CRT group experienced significant improvement in NYHA class ($p = .03$) and SRV fractional area of change (FAC) (pre 22% vs CRT 30.7%, p = .03). Multivariate subanalyses demonstrated that chronic subpulmonary LV pacing was associated with SRV dysfunction (HR = 2.7 (10–7.0)) and SRV dilatation (HR = 4.7 (1.1–20.6)) which eventually resulted in deterioration of functional status. These undesirable effects were not observed in the CRT group, raising the question of whether CRT should be considered in SRV patients requiring ventricular pacing, even in the absence of baseline RV dysfunction.

Another single center study included 4 TGA patients (age 31.5 years [9–47]) with a median follow-up of 4 years after implantation of a CRT device (epicardial CRT-system: $n = 3$, transvenous CRT-system: $n = 1$).[20] Another novel definition of CRT response was introduced. Responders were defined as those with >7% increase in systemic blood pressure between CRT on versus off during the perioperative period, >5% decrease in cardiothoracic ratio or improvement in NYHA class. Despite a decrease in QRS duration, none of the patients met any of these criteria and thus all 4 patients were classified as non-responders. More recently, the same authors expanded their cohort and introduced another novel definition to identify responders [21]. In the presence of ventriculography during follow-up, responders were classified as having a <15% decrease in SRV end-systolic volume index. In the remaining patients in whom ventriculography was unavailable, responders were defined as patients with a >5% decrease in cardiothoracic ratio or improvement in NYHA class. Of the 27 included CHD patients, 8 had an SRV (baseline characteristics not further specified). Four patients were labeled as responders, of whom 1 did not have symptoms of heart failure at baseline and 2 patients had no SRV conduction delay. Non-optimal lead position (not further specified) in 2 patients was considered as another explanation for no response. Shortening of QRS duration, indicating improved electrical synchronization, did not result in clinical improvement. The severity of systemic atrioventricular valve function was not reported.

More recently, Karpawich et al. used an invasive measure of contractility (dP/dt-max) with a catheter within the SRV as a pre-implant screening tool in CHD patients[45]. Six DTGA and 2 CCTGA adult patients (age 25 [24–39]) showed an initial dP/dt-max improvement of ≥15% and received CRT. During a median follow-up time of 2.7 years, hemodynamic benefits of CRT persisted in all patients. Hence, this study

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Table 1
Studies on CRT in patients with SRV.

Author	Total SRV patients included n=	DTGA (n,%)	CCTGA (n,%)	Total patients with available data	Age [range] (y)	M/F (n/n)	Fu [range] (y)	Clinical improvement (%)	Non-responders (%)	Mortality (%)	Definition CRT-responder	Comments
Yin (2019)[26]	15	2 (13)	13 (87)	15	NA	NA	5.7 ± 3	NA	60	NA	≥5% absolute increase in SRV function or FAC	Only adult patients included
Moore # (2019)[38]	6	3 (50)	3 (50)	6	48 [36–73]	3/3	0.9 [0.2–1.9]	100	0	0	Echocardiographic improvement in SRV function (≥10% increase in FAC) or improvement in NYHA functional class by ≥1 category	First report on hybrid transcatheter-surgical lead implantation in patients with SRV utilizing endocardial mapping to determine latest activation site.
Flügge* (2018) [44]	13	5 (38)	8 (62)	2	59.5 [50–69]	2/0	6.6 [3.2–10]	100	0	50	No definition reported	German registry
Koyak* (2018)[25]	10	NA	NA	10	NA	NA	NA	60	40	NA	Improvement in NYHA functional class and/or SRV EF by ≥1 category	First study including only adult patients
Moore # (2018)[37]	20	0	20 (100)	20	40 ± 15	10/10	4.6	67	33	0	Sustained improvement in NYHA functional class by ≥1 class or echocardiographic improvement in SRV function (≥10% increase in FAC) for patients with baseline NYHA class ≥2	First study focusing on technical considerations for lead implantation in CCTGA.
Karpawich (2017)[45]	8	6 (75)	2 (25)	8	28 [24–39]	8/0	2.7 [1−12]	100	NA	NA	Acute improvement in dP/dt-max of ≥15% was used as a selection criteria to determine patients eligible for CRT	Only patients with ≥15% increase of dP/dt-max after biventricular pacing underwent CRT implantation.
Miyazaki (2016)[20]	4	1 (25)	3 (75)	4	31.5 [9–47]	NA	4 [0.2–5.9]	0	100	0	>7% increase in the SBP after turning on CRT mode in the perioperative period or > 5% decrease in CTR or improvement in NYHA class	
Miyazaki (2019)[21]	8	NA	NA	8	NA	NA	NA	50	50	0	<15% in SyVESVI measured on angiography In patients without angiography during follow-up: >5 decrease in CTR or improvement in NYHA functional class	
Yeo # (2013)[19]	7	0	7 (100)	7	46 ± 10	NA	2 ± 1	NA	NA	NA	No definition reported	Data is not specified per patient, however significant improvement in mean NYHA class and SRV function was observed.
Janousek* (2009)[24]	36	12 (33)	20 (56)	27	28.8	NA	0.6	NA	14	NA	Improvement in SRF function EF/FAC and no decrease in NYHA functional class	Largest multicenter study. Data not specified per patient, however mean NYHA class and SRV function improved.
Jauvert # (2009)[18]	7	5 (71)	2 (29)	7	24.6 ± 12	4/3	1.6 ± 0.7	100	0	14	No definition reported	
Cecchin (2009)[17]	9	NA	6 (67)	9	27 [0.5–43]	NA	>3 months	NA	67	22	≥10% increase in SRV EF (objective) or improvement in NYHA functional class by ≥1 category (subjective)	
Dubin* (2005)[23]	17	4 (24)	13 (76)	17	12.7 [4.9–50]	NA	NA	76	NA	0	Improvement in SRV EF measured on echocardiography (not further specified)	First multicenter study on CRT in CHD.
Janousek # (2004)[16]	8	4 (50)	3 (38)	8	12.5 [7–29]	NA	1.5 [0.6–1.6]	NA	NA	0	No definition reported	First study reporting on outcomes of CRT in patients with SRV. Data not specified per patient, however mean NYHA class and SRV function improved.

CCTGA = Congenitally corrected transposition of the great arteries, CTR = Cardio-thoracic ratio, DTGA = dextro transposition of the great arteries, EF = Ejection fraction, FAC = Fractional area change, F = female, Fu = Follow-up, M = male, NA = not available, NYHA = New York Heart Association, SyVESVI = systemic ventricular endsystolic volume index, SRV = Systemic right ventricle, y = year, * = Multicenter study/registry, # = Only SRV patients included.

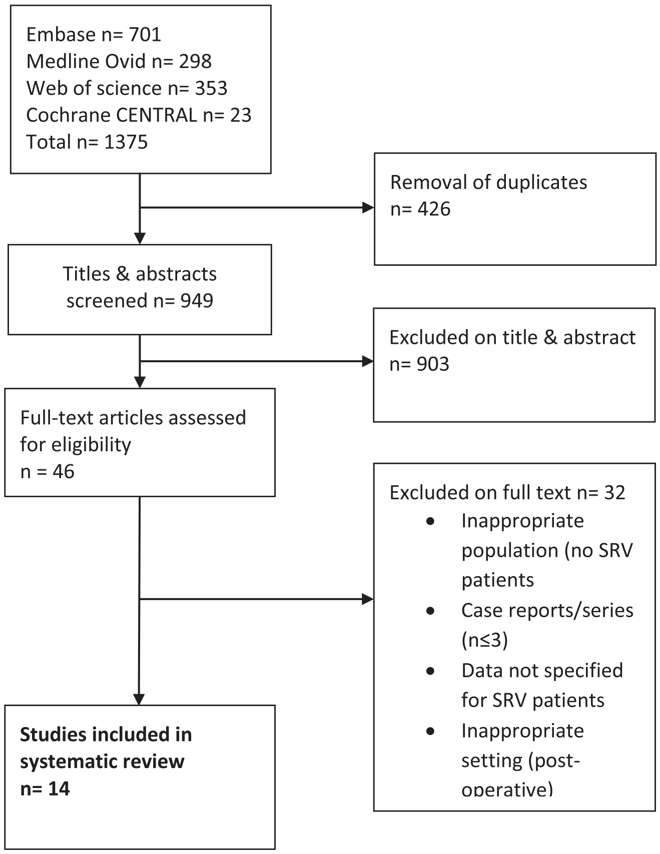

Fig. 1. PRISMA flowchart demonstrating selection of papers reporting on outcomes of cardiac resynchronization therapy in patients with a systemic right ventricle.

demonstrated that invasive dP/dt-max measurement could be a promising diagnostic tool for patient selection.

The largest single center study to date on CRT in CCTGA focused not only on clinical outcome, but also on technical challenges associated with CCTGA anatomy during transvenous CRT implantation [22]. Responders were defined as patients with baseline NYHA class ≥2 demonstrating sustained improvement in NYHA class by at least 1 grade or an increase in SRV FAC of ≥10% within 3 months after CRT. Of 20 patients (age 40 ± 15 years), 12 patients had symptomatic congestive heart failure. Of the patients with congestive heart failure, acute improvement was observed in 67% ($n = 8$), but 25% ($n = 2$) showed loss of response during a median follow-up period of 4.6 years. Of the 8 asymptomatic patients, only 1 experienced progressive heart failure and underwent heart transplantation after 12 years. After 7.7 years of follow-up, the remaining 7 patients had minimal symptoms. These findings, substantiate the results reported by Janousek et al. [16], indicating that CRT may be effective in "preventing" progression of SRV failure. Despite anatomical challenges, transvenous lead placement attempts were successful in all but one CCTGA patient. Leads were positioned within either basal or mid-RV body ($n = 12$, 60%) or RVOT ($n = 8$, 40%). Patients with an RVOT lead appeared to have lower CRT response (HR = 7.1, $p = .026$).

Finally, a new technique for hybrid transcatheter-surgical lead implantation was introduced. Six patients underwent detailed *endo-* and epicardial electro-anatomical SRV mapping followed by epicardial lead placement. CRT response was defined as improvement in SRV function with ≥10% in FAC or an improvement in NYHA class by at least 1 grade. All patients showed improvement in NYHA class and significant reduction in median QRS duration (193 to 147 ms, $p < .001$). All but one patient showed improvement in FAC; of whom 5 patients demonstrated even an improvement of ≥10%. After a median follow-up time of 11 months (IQR 5–14 months), 2 out of 3 patients who were initially referred for heart transplant no longer fulfilled the criteria for transplantation. Larger, long-term follow-up studies are essential to determine the future role of hybrid CRT implantation in this population.

3.2. Multicenter studies

The multicenter studies investigating CRT efficacy in SRV patients report promising outcomes with low non-responder rates [23–25]. Dubin et al. reported a multi-center experience of both CHD and acquired heart disease pediatric and adult patients that included 17 SRV patients (12.7 years [4.9–50]). Seventy-one percent (12/17) were identified as responders (defined as showing any increase in RV ejection fraction) [23]. Thirteen patients also showed improvement in NYHA class. The number of adult patients included was not specified, nor was the outcome specified for patients with transvenous systems versus epicardial/mixed systems. Adverse events among transvenous versus epicardial/mixed systems were similar at early (22% vs. 17%, respectively) and late (15% vs. 5%) time points among the total cohort of 103 CHD patients.

Another mixed retrospective multicenter study of CHD and acquired heart disease included 27 SRV patients with a median follow-up of 7.3 months and reported a non-response rate of only 13.6% [24]. SRV patients showed a less favorable outcome of CRT and a higher degree of systemic atrioventricular valve regurgitation compared to patients with a systemic LV (SLV). The difference in response could be explained by variation in underlying mechanism of systemic atrioventricular valve regurgitation, SRV anatomy and physiology, prior cardiopulmonary bypass, and higher burden of atrial arrhythmia. Hence, surgical correction of severe systemic atrioventricular valve regurgitation in combination with CRT was highlighted as a potential efficient treatment strategy in SRV patients.

3.3. Studies reporting exclusively GUCH patients with an SRV

The above-mentioned studies examined mixed populations including both pediatric and adult patients. Koyak et al. were the first to publish outcomes of CRT in an exclusively adult cohort including 10 SRV patients (median age 40 years) [25]. Patients showing either improvement in NYHA class or in SRV ejection fraction by at least one category, were classified as CRT responders. The median follow-up duration of the total cohort was 2.6 years and was not specified for the SRV group separately. Four patients showed clinical improvement and 2 in SRV echocardiographic function, yielding a response rate of 60%. There was no significant decrease in QRS duration (pre CRT 162 ± 44 ms vs. post CRT 157 ± 25 ms). Less favorable long-term outcomes were reported by another single-center study conducted by Yin et al. who also focused on exclusively adult SRV patients. After long-term follow-up (4–5 years), 40% of the patients were identified as CRT responders, defined as ≥5% absolute increase in SRV function or FAC [26].

4. Discussion

4.1. Summarizing current experience where guidelines do not apply

The goal of this systematic review is to summarize studies reporting the available data for CRT in SRV patients, as current guidelines lack clear recommendations for this patient group. In general, heterogeneity in sample size, cohort composition and definitions to measure CRT efficacy was striking (Table 1). Uniform nomenclature for definitions for 'responders' and 'non-responders' is essential when comparing study outcomes. For example, of the two large multicenter studies to date, the former defined 'non-responder' as either no change or deterioration in SRV function [23] while the latter defined 'non-responder' as either no change or deterioration in SRV function *and* no clinical response defined as a decrease in NYHA class [24]. Besides changes in echo- and electrocardiographic parameters, the latter study also included clinical

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response when defining '(non-)responders'. Uniform worldwide consensus on defining 'responders' and 'non-responders' is essential to compare outcomes of CRT in this challenging patient population.

Based on most of the retrospective collected data included in this review, the European working group on CHD recommends that CRT *can* be considered in patients in NYHA class ≥ II, impaired systemic right ventricular function (ejection fraction ≤35%) and right bundle branch block QRS morphology (>150 ms, spontaneous or paced) [27]. Importantly, this excludes CCTGA patients with left-sided RV failure who typically display a LBBB pattern. So far, most studies have reported outcomes of CRT therapy in mixed populations with limited follow-up data. At present, long term outcomes, clinical profiles, influence of lead location and identification of risk factors predicting therapy failure remain unknown.

4.2. Systemic right ventricle

The RV clearly differs in embryological origin, anatomy, functional properties and electrophysiological characteristics as compared to the LV. The crescent-shaped RV is wrapped around the LV, has a unique longitudinal activation pattern, lower oxygen requirement and lower coronary blood flow compared to the LV [28]. The RV, normally supporting the low-pressure pulmonary system, is prone to fail when supporting the systemic circulation. In contrast to SLV failure, less is known regarding the pathophysiology and outcomes of different therapeutic options in patients with SRV failure. Moreover, SRV failure is an important predictor of long-term morbidity and mortality. An SRV is encountered in patients with DTGA and previous Mustard or Senning operation or CCTGA. Clinically, these are different entities with differences in anatomy, physiology, surgical history and hence scar tissue and the coexistence of atrial and ventricular tachyarrhythmias which may influence outcomes of CRT [29–31].

CCTGA is characterized by atrio-ventricular and ventriculo-arterial discordance and is often associated with additional cardiac anomalies, such as ventricular septal defect, pulmonary valve stenosis, Ebstein anomaly and spontaneous atrioventricular conduction disturbances. In the absence of these additional cardiac anomalies, patients may be asymptomatic in early life and heart failure usually develops around the 4th decade of life. D- and CCTGA patients have a risk for multiple re-operations due to residual defects or valvular dysfunction, pacemaker implantation and increased scar tissue predisposing these patients to atrial and ventricular tachyarrhythmias. Systemic atrioventricular valve regurgitation or residual shunts may re-inforce SRV failure by ventricular dilation resulting in progressive functional decline. Particularly in CCTGA patients with an intrinsically abnormal Ebsteinoid systemic atrioventricular valve, progressive regurgitation and subsequent SRV volume overload and dilatation may ensue [32]. In addition to the surgical risk, patients with CCTGA have abnormal shift of the atrioventricular septum, with abnormal position of the conduction system. This predisposes to the risk of atrioventricular conduction disturbance, often necessitating pacemaker implantation. Yeo et al. demonstrated that chronic univentricular subpulmonary LV pacing in CCTGA patients predicted long-term deterioration of SRV function and NYHA class [19]. In a similar study, Horovitz et al. evaluated the long-term effects of chronic LV pacing in DTGA patients on cardiac function, ventricular dyssynchrony and functional status [33]. Again, long-term chronic LV pacing was associated with decreased functional status, impaired SRV function and enhanced inter- and intraventricular dyssynchrony. Future randomized studies are needed to determine the role of CRT in preventing pacing induced ventricular dysfunction in this vulnerable CHD population.

4.3. Anatomical challenges during SRV lead implantation

Understanding the underlying anatomy of the coronary venous system is essential when considering CRT in SRV patients. In CCTGA patients, the coronary sinus, which is the gateway for ventricular lead implantation, drains predominantly from the SRV. To date, studies examining individual variations in the anatomy of the coronary sinus ostia are scarce [34]. Recently, Moore et al. examined the coronary venous anatomy in 19 CCTGA patients undergoing transvenous SRV lead implantation [22]. In line with data from the largest post-mortem study [35], the coronary venous anatomy differed from conventional ($n = 7$), with separate ostia (n = 7), dual ostia ($n = 3$) or venous drainage through the vein of Marshall ($n = 2$). A transvenous approach was still successful in 18 patients (95%) indicating that despite anatomical variations, this approach is feasible for most CCTGA patients. Both computed tomographic (CT) and magnetic resonance imaging (MRI) can be used for appropriate pre-procedural planning [36]. In addition, correlating the coronary venous anatomy with segmental wall motion abnormalities defined by echocardiography or (non-) invasive ventricular activation mapping may provide relevant anatomical and functional information to determine optimal lead location.

4.4. Optimal lead location

Despite increasing experience, optimal lead location for both percutaneous and epicardial lead implantation has not been defined. Empiric lead placement or lead positioning at the latest site of ventricular activation are commonly used strategies in clinical practice. Except for one, none of these studies, performed subanalyses on the various lead locations and CRT response. In a cohort of 20 patients, the final lead position was within the basal or mid-RV body in 12(60%) patients and RVOT in 8 (40%)[37]. Patients with an RVOT lead appeared to have higher rate of heart failure development despite successful CRT (HR = 7.1, $p = .03$). The RVOT was only targeted in an attempt to achieve maximum interlead distance or when no other suitable location could be found. As SRV contraction relies primarily on circumferential rather than longitudinal shortening, the authors pointed out that pacing at the right ventricular outflow tract (RVOT) may be inferior to mid ventricular pacing. Differences in CRT responses between patients with a transvenous CRT system and a mixed/epicardial CRT system also remain unknown.

Recently, the same research group reported the hybrid transcatheter-surgical CRT approach in order to reduce surgical exposure and morbidity while retaining benefits of precise localization of the latest epicardial activation site[38]. Optimistic outcomes were reported on short-term (11 months), but long-term outcomes in a larger population are required to substantiate their findings. Various other strategies such as empiric lead placement, temporary RV pacing at putative sites and localization of areas of mechanical dyssynchrony by angiography are also used in clinical practice. At present, it remains unknown whether the different lead placement strategies result in different outcomes.

4.5. Parameters for CRT response

Currently, there are no uniform criteria to identify CRT responders, nor are there any pre-defined outcomes to measure efficacy of CRT in SRV patients. Strikingly, most studies focus more on improvement in 'numbers' rather than functionality and quality of life.

All studies included echocardiographic parameters to measure CRT response. Although echocardiography is a well-established diagnostic tool to assess SLV function, its use to quantify RV function, and especially SRV function is extremely challenging and therefore often inaccurate. The complex geometry, altered loading conditions and the anatomical positioning affect the reliability and reproducibility of echocardiographic SRV assessment. Furthermore, atrial conduits, septal patches and residual shunts additionally affect the accuracy of echocardiographic SRV assessment. When precise quantitative ventricular data are required, cardiac magnetic resonance (CMR) is considered as the diagnostic modality of choice [39]. However, in many SRV patients with a pre-existing pacemaker or internal cardiac defibrillator, use of CMR is

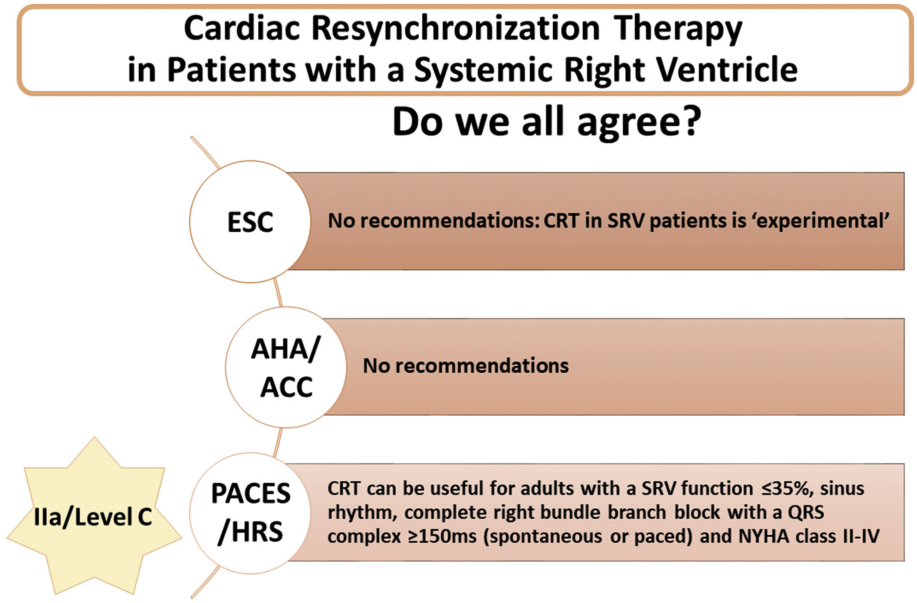

Fig. 2. Overview of the ESC, AHA/ACC and the PACES/HRS Expert Consensus recommendations. AHA/ACC = American College of Cardiology/American Heart Association, ESC = European Society of Cardiology, PACES/HRS = Pediatric and Congenital Electrophysiology Society (PACES)/Heart Rhythm Society.

precluded. QRS duration is also considered as an important electrocardiographic variable to determine CRT efficacy. Based on the studies included in this systematic review, not all SRV patients with shortening of QRS duration showed improvement in mechanical contraction and functional status. Several other studies performed in patients with ischemic cardiomyopathy demonstrated that mechanical resynchronization rather than QRS duration is a better predictor for CRT response [40,41]. Whether this also accounts for CHD patients and more specific SRV patients, still remains to be investigated.

Finally, NYHA classification is commonly used to monitor functional status of patients with heart failure. Studies included in this review, solely reported NYHA class when assessing the functional status. On the one hand, NYHA class is easy to use in clinical practice, on the other hand, elements of patient and doctor subjectivity are inevitable. Diller et al. were the first to assess the relationship between objective exercise capacity and NYHA class in 335 GUCH patients [42]. The study outcomes showed that indices of cardiopulmonary exercising such as peak Vo2 are superior to patient reported heart failure symptoms. This data highlights the important additional value of objective exercise testing during follow-up of GUCH patients with CRT.

Although CRT has been applied in SRV patients for more than 15 years, there are no uniform criteria or consensus defining responders and non-responders. Response rates vary in current literature and are highly dependent on the criteria used (Table 1). Future studies are recommended to focus on a homogenous group and distinguish between improvement in functional state (subjective versus objective), electrocardiographic changes (QRS duration), echocardiographic changes (FAC, ventricular dimensions, ejection fraction etc.) but also quality of life. Surprisingly, to date, there are no studies examining quality of life or simple results of 6-min walk test in SRV patients with CRT. Reporting all these outcomes separately in future studies, will hopefully result in more accurate criteria to identify CRT responders in this unique and challenging population.

5. Limitations

Lack of clear recommendations in guidelines may have resulted in variability in center-specific policies. In addition, depending on patient volumes, the level of expertise may also differ between centers. Also, there are no uniform pre-selection criteria nor pre-defined measures to examine efficacy of CRT therapy. Centers used non-uniform definitions to identify 'responders' which subsequently impairs reliable comparison of study outcomes. Echocardiographic assessment of SRV dimensions and function is extremely challenging, thereby possibly affecting its validity and reproducibility.

6. Conclusion and future perspectives

This systematic review summarizes outcomes of CRT in patients with an SRV. Regardless of limitations of the studies included in this review, data indicates that CRT can be an effective treatment for patients with a failing SRV. Guidelines are cautious with CRT recommendations as evidence supporting CRT in this population has been limited to relative small studies in which adults and pediatric patients with different underlying defects, including chanelopathies and cardiomyopathies, are included. Importantly, long-term outcomes are also lacking. Due to the aforementioned reasons, recommendations on CRT in SRV patients are absent in the ESC and AHA/ACC guidelines [12,13]. PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult CHD has attempted to provide clinical guidance (Fig. 2) [43]. However, these recommendations are mainly extrapolated from large cohorts of patients with ischemia induced heart failure. Future studies are essential to further elucidate and substantiate the abovementioned guidelines. Uniform nomenclature is essential in order to reliably compare outcomes of studies. Hence, when reporting on outcomes of CRT in patients with CHD, the following features are recommended:

- Amount: A sufficient number of patients, ideally in the form of a large multicenter study dedicated to SRV patients and eventually in the form of a prospective registry, is needed to perform sophisticated risk analysis.
- Distinction: Distinction between pediatric-adults, short- and long-term outcomes, systemic left- and systemic right ventricle, transvenous- and epicardial lead systems, final lead locations and sex differences are essential for clinical guidance.
- Clarification: Clarify definition of 'responders' and distinguish between outcome in functional class (subjective/objective), electrophysiological- and electrocardiographic changes. Advances in

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cardiac imaging have resulted in numerous parameters assessing ventricular functionality, dimensions and interventricular dyssynchrony which are used alternately in studies evaluating CRT in GUCH thereby hampering comparison of study outcomes. In summary, when defining 'responders' it is important to differentiate between improvement in 'numbers', symptoms and quality of life.

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Declaration of Competing Interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.06.052.

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