Effects of cardiac resynchronization therapy on echocardiographic indices, functional capacity, and clinical outcomes of patients with a systemic right ventricle

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Aims	Surgically (SC) or congenitally corrected (CC) transposition of the great arteries (TGA), associated with a systemic right ventricle (RV), is often complicated by heart failure. This retrospective study assessed the functional and mechanical effects of cardiac resynchronization therapy (CRT) in patients presenting with TGA.
Methods and results	Seven patients with SC ($n = 5$) or CC ($n = 2$) TGA (mean age 24.6 $\pm$ 12 years), a failing systemic RV, and intraventricular dyssynchrony, underwent implantation of a CRT-P. Permanent pacemakers were previously implanted in five patients. The leads were implanted by a combined transvenous and epicardial approach in the five patients with SC TGA. Echocardiography, including tissue Doppler imaging and cardiopulmonary exercise testing were performed before and during CRT. Since, in all patients, ventricular dyssynchrony was due to delayed septal wall contraction, the interventricular septum and RV free wall were stimulated synchronously, with a view to resynchronize a maximum amount of myocardium. After 19.4 $\pm$ 8.1 months of CRT, mean QRS duration decreased from 160 $\pm$ 31 to 120 $\pm$ 28 ms ($P = 0.03$), intraventricular delay from 104 $\pm$ 27 to 14 $\pm$ 15 ms ($P = 0.01$), New York Heart Association functional class from 3.0 to 1.57 ($P = 0.01$), and peak oxygen consumption increased from 13.8 $\pm$ 2.5 to 22.8 $\pm$ 6.7 mL/kg/min ($P = 0.03$). One patient died suddenly at 23 months of follow-up.
Conclusions	CRT was technically feasible and associated with improvements in cardiac mechanical function and clinical status in patients with TGA, failing systemic RV, and intraventricular dyssynchrony.
Keywords	Cardiac resynchronization therapy • Intraventricular dyssynchrony • Great arteries transposition • Heart failure • Right ventricular failure

Introduction

Cardiac resynchronization therapy (CRT) is highly effective in a majority of patients presenting with symptomatic heart failure (HF) and cardiac mechanical dyssynchrony refractory to optimal medical treatment.[1–3] Tricuspid regurgitation and acute failure of the systemic right ventricle (RV) are common fatal complications in adults with surgically (SC) or congenitally corrected (CC) transposition of the great arteries (TGA). Supraventricular tachyarrhythmias may also cause sudden death.[4] CRT to support the failing RV has been associated with encouraging short-term haemodynamic results in patients with SC TGA.[5–8] The aim of our study was to examine: (i) the role of echocardiography in the selection of candidates for CRT; and (ii) the long-term electromechanical effects of CRT in patients presenting with SC or CC TGA.

Patient population and methods

The study included consecutive patients presenting with SC or CC TGA at the Hôpital Necker, Paris, France, who underwent

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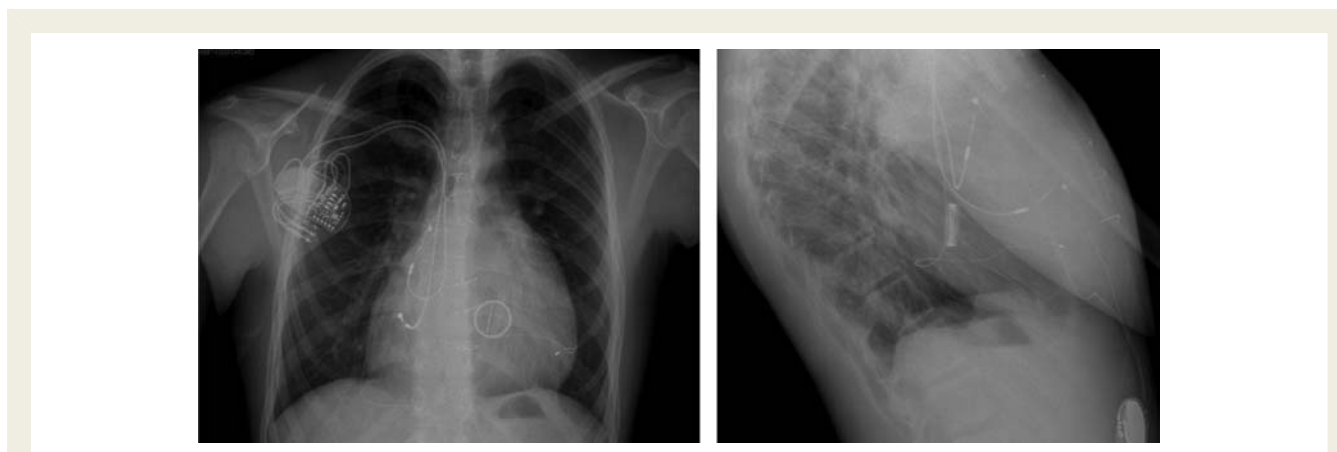
Figure 1 Lead placement in patient No. 7. All leads were implanted transvenously. The LV lead was implanted on the septum and the RV lead in the mid-portion of a lateral vein.

implantation of CRT systems on the basis of clinical, electrocardiographic, and echocardiographic criteria commonly applied in cases of HF due left ventricular (LV) dysfunction.[9] Specifically, we considered patients to be candidates for CRT if they: (i) were in New York Heart Association (NYHA) functional class III or IV despite optimal medical treatment; (ii) had a >120 ms QRS duration; and (iii) had echocardiographic findings of intra- and interventricular (VV) dyssynchrony.

Study protocol

Before implantation of the CRT system, the patients underwent clinical evaluation, including a surface electrocardiogram, measurement of oxygen uptake at peak exercise (VO_2 max) and a transthoracic echocardiogram. The same evaluation was performed at least 2 months after the implant procedure, and yearly thereafter. The results of the last echocardiogram and last measurement of VO_2 max in each patient were used for comparative analyses. However, since patients No. 1 and No. 5 were unable to exercise before undergoing the CRT implant procedure, the results of their follow-up exercise tests were not included in the analysis.

Echocardiographic study

Echocardiograms were performed using a Vivid™ Cardiovascular Ultrasound system with a 3.5 MHz transducer (General Electric Health Care-Vingmed, Erlangen, Norway). The imaging data were analysed offline with an EchoPAC™ 6.1 clinical workstation (General Electric-Vingmed). The same recordings, using the same protocol, were made before and after CRT system implantation.

Interventricular dyssynchrony, defined as a VV delay >40 ms, was assessed by: (i) measurement of the systemic pre-ejection interval, i.e. the delay between the onset of the QRS complex and the onset of aortic outflow; (ii) measurement of the pulmonary pre-ejection interval, i.e. the delay between the onset of QRS and the onset of pulmonary outflow; and (iii) calculation of the VV mechanical delay, i.e. the difference between systemic and pulmonary pre-ejection intervals.

Intraventricular dyssynchrony was defined as a ≥60 ms delay between activation of the septum and that of the free wall of the RV. Measurements made in the assessment of intraventricular dyssynchrony included: (i) delay between QRS onset and aortic valve closure timing, which corresponds to the duration of systemic systole; (ii) delays between (a) onset of QRS and end of septal contraction (septal delay), and (b) onset of QRS and end of the RV free wall contraction (lateral delay), using colour M-mode and tissue Doppler imaging; (iii) post-systolic contraction time (or diastolic contraction), i.e. the difference between aortic valve closure timing and end of septal or RV free wall contraction; (iv) RV diastolic filling time (DFT)/RR interval ratio; and (v) visual estimates of (a) tricuspid regurgitation (graded from 1 to 4) and (b) systolic performance of the RV.

Exercise testing

Exercise tests were performed on treadmill, using the Bruce protocol, for measurement of oxygen uptake at peak exercise (VO_2 max).

Implantation techniques and device programming

In patients presenting with CC TGA, the normal position of the coronary sinus allowed the implantation of the CRT systems via an exclusively endocardial approach (*Figure 1*). Angiograms performed before the implant procedure confirmed the accessibility of the coronary sinus and its tributary veins. In patients presenting with SC TGA, the leads were implanted by combined transvenous and surgical approaches. Since the coronary veins are located along the subpulmonary free wall of the LV, Capsure Epi® model 4468 epicardial, steroid eluting, bipolar pacing leads (Medtronic Inc., Minneapolis, MN, USA) were implanted on the mid-portion of the RV free wall, via limited lateral thoracotomy, then tunnelled to a left prepectoral cutaneous pocket and connected to the pulse generator. The right atrial and LV leads were implanted transvenously.

Except in patients who were in atrial fibrillation (AF), the sensed or paced atrioventricular (AV) delay was optimized by echocardiography. The optimal AV delay was defined as the shortest interval associated with the longest RV DFT, with an A-wave as distinct as possible from the E-wave and not prematurely truncated by

Table 1 Baseline characteristics of seven patients with SC or CC TGA

Patient no.	Age (years)	Gender	Prior operation	Pacing mode before CRT	Underlying rhythm
1	50	M	NA[a]	–	Atrial fibrillation
2	27	F	Mustard	DDD-R	Sinus node dysfunction, complete AV block
3	20	M	Senning	VVI-R	Sinus node dysfunction
4	15	M	Senning	DDD-R	Sinus node dysfunction
5	24	F	Senning	VVI-R	Atrial fibrillation, complete AV block
6	20	W	Senning	–	Sinus rhythm
7	16	F	NA[a]	DDD-R	Sinus node dysfunction, complete AV block

CRT, cardiac resynchronization therapy; AV, atrioventricular.
[a]Congenitally corrected.

RV systole. AV delay scanning achieved an optimal AV delay ascertained by the tricuspid flow pattern, without loss of complete LV capture. The ventricles were paced synchronously in all patients.

Statistical analysis

The results are expressed as means $\pm$ standard deviation. Changes in quantitative variables between baseline and follow-up were compared using the Wilcoxon signed-rank test. A *P*-value <0.05 was considered statistically significant.

Results

Between January 2003 and April 2006, among 83 consecutive patients presenting with SC or CC TGA, 17 who had hypokinetic systemic RV were screened for CRT. Among these 17 patients, nine were in NYHA class I or II, of whom four had received permanent dual chamber pacemakers, and four had preserved spontaneous AV conduction. One additional patient had a permanent single chamber pacemaker for complete AV block, though had no induced cardiac dyssynchrony. A single non-paced patient, who was in NYHA functional class II, had a QRS >120 ms and echocardiographic indices of intraventricular dyssynchrony similar to those observed in patients selected for CRT. One patient was in NYHA functional class III without any of the indices of dyssynchrony described earlier.

Ultimately, four men and three women (mean age = 24.6 $\pm$ 12 years) met our criteria for implantation of CRT systems, including two patients with CC and five patients with SC TGA, who had undergone Senning's ($n = 4$) or Mustard's ($n = 1$) procedures in childhood. All patients were in NYHA functional class III at the time of CRT system implant. At least 1 year earlier, two patients had undergone surgery aiming at improving haemodynamic function, and consisting of pulmonary artery banding in patient No. 4, and tricuspid valve replacement in patient No. 7. The main baseline characteristics of the seven patients are summarized in *Table 1*.

Management of the pacing systems and implant procedures

Among five permanently paced patients, three (No. 2, 5, and 7) had developed complete AV block after surgical repair of TGA, and two (No. 3 and 4) had developed sinus node dysfunction and prolonged AV conduction. Patient No. 4 was the recipient of a dual chamber pacemaker, while patient No. 3 was paced in VVI mode at the RV epicardium, because of superior caval canal obstruction and difficulties in implanting an atrial endocardial lead. He has since undergone a revascularization and stenting procedure that enabled transvenous RV pacing.

In patients who were permanently paced before CRT, the pulse generator was removed and replaced.

An Insync® III 8042 (Medtronic) CRT-P was implanted in six patients, and a Pulsar® max 1274 DDD-R pacemaker (Guidant, Boston Scientific Corporation, Natick, MA, USA) in patient No. 1. In that very first patient, who was in permanent AF, the RV lead was connected to the atrial, and the LV lead to the ventricular channel of the pulse generator, and the AV delay was programmed to its minimum value of 10 ms to provide nearly synchronous biventricular pacing. In France, in 2003, candidates for CRT who were in AF were likely to receive a dual chamber pacemaker. Though such a device was not dedicated to CRT, it enabled: (i) biventricular pacing from two separate channels; and (ii) the programming of two different outputs, without incurring the risk of ventricular pacing inhibition in case of lead dislodgement into the right atrium (with possibly serious consequences for patients whose AV junction had been ablated). Sensing and refractory periods could be appropriately programmed separately to avoid VV cross-talk. In all patients who were permanently paced before CRT, the previously implanted LV lead, usually at the apex, was capped, abandoned and replaced by a lead affixed to the VV septum, while the RV lead was implanted on the free wall. In this group of patients, baseline septal contraction, delayed by a mean of 504 $\pm$ 51 ms after the QRS onset continued for a mean of 89 $\pm$ 29 ms after the onset of diastole, whereas the duration of RV free wall contraction (400 $\pm$ 52 ms) and duration of systemic systole (415 $\pm$ 43 ms) were nearly equal. In an effort to pace most of the RV myocardium simultaneously, the ventricular leads were placed as far apart as possible. In patient No. 3, who had received a VVI-R pacemaker for sinus node dysfunction, an atrial lead was implanted to restore AV synchrony. In patient No. 5, who was in permanent AF, the atrial channel of the CRT-P was capped.

We observed no procedure-related complication. Patient No. 2 underwent replacement of the first CRT-P by a Frontier II® pulse generator (Saint Jude Medical, Sylmar, CA, USA) at 30 months

after implant because of rapid battery drain due to a high epicardial RV capture threshold.

Changes in functional capacity

The main study results observed in each individual patient are listed in *Table 2*. Between baseline and repeat evaluations, performed at a mean of 19.4 ± 8.1 months of follow-up, the mean NYHA functional class decreased from 3.0 to 1.6 ± 0.5 ($P = 0.01$), and VO_2 max rose from 13.8 ± 2.5 to 22.8 ± 6.7 mL/kg/min, ($P = 0.03$).

Electrocardiographic and echocardiographic observations

QRS duration (*Table 3*) decreased significantly, from 160 ± 31 to 120 ± 28 ms ($P = 0.007$). Although the indices of VV dyssynchrony did not change significantly, intraventricular and septal delays were both significantly shortened (*Table 3*). The lateral delay, however, was not changed significantly. Therefore, the post-systolic contraction of the septal wall was eliminated, such that septal contraction ended simultaneously with closure of the aortic valve, the timing of which was 415 ± 43 ms at baseline and 409 ± 24 ms during follow-up. A representative example (patient No. 7) is shown in *Figure 2*. RV DFT increased markedly, and RV DFT/RR increased from 38.3 ± 5.7 to 46.6 ± 4.3 ($P = 0.06$), as diastolic contraction was shortened from 89 ± 29 ms at baseline, to -11 ± 15 ms during follow-up ($P = 0.01$). The tricuspid regurgitation grade decreased from 1.6 ± 1.3 before to 1.2 ± 1.1 during CRT, a statistically non-significant difference.

Clinical outcomes

Over a mean follow-up of 19.4 ± 8.1 months, all patients improved clinically. It is noteworthy that diuretics were discontinued in three patients. Beta-adrenergic blockers were continued in the same doses in four patients, increased in two, and introduced in one patient, while treatment with angiotensin converting enzyme inhibitors was unchanged in six patients and increased in one.

Patient No. 1, who was 50 years old at the time of implant, died suddenly 23 months after the onset of CRT. This patient, who had a normal coronary angiogram before and no known ventricular arrhythmia before and during CRT, was in permanent AF, with 30% spontaneous AV conduction, despite a back-up pacing rate programmed at 70 b.p.m. Therefore, he underwent AV node ablation at 12 months after implant of the CRT system to facilitate complete biventricular capture, which alleviated the manifestations of HF. Since the implanted device was not interrogated, the cause of sudden death was not clarified.

Discussion

Main findings of the study

Echocardiographic changes

Our detailed echocardiographic observations indicate that CRT markedly improved cardiac mechanical function in appropriately selected patients presenting with SC or CC TGA, advanced HF refractory to medical therapy, and cardiac mechanical dyssynchrony. Intraventricular dyssynchrony, invariably due to a delayed

Table 2 Main individual study results

Patient No.	FU duration (months)	QRS duration (ms)		NYHA FC		VO₂ max (mL/kg/min)		Lateral delay (ms)		Septal delay (ms)		Spatial dyssynchrony (ms)		DFT/RR (%)	
		Baseline	FU	Baseline	FU	Baseline	FU	Baseline	FU	Baseline	FU	Baseline	FU	Baseline	FU
1	23	140	140	3	2	–	–	350	390	490	390	140	0	34	44
2	26	160	80	3	1	12	16	400	420	520	430	120	10	33	43
3	23	200	140	3	1	12.5	31	410	410	510	400	100	10	36	47
4	21	160	100	3	2	14	17	430	420	490	390	60	30	50	55
5	27	140	120	3	2	–	–	380	380	490	390	110	10	40	45
6	7	120	100	3	2	18	22	340	350	430	350	90	0	38	43
7	9	200	140	3	1	12.4	28.2	490	430	600	390	110	40	45	49
Mean ± SD	19.4 ± 8.1	160 ± 31	120 ± 28	3	1.6 ± 0.5	13.8 ± 2.5	22.8 ± 6.7	401 ± 52	400 ± 28	504.3	391 ± 28	104 ± 27	14.3 ± 15.1	38.3 ± 5.7	46.6 ± 4.3

FU, follow-up; NYHA FC, New York Heart Association functional class; VO₂ max, maximum oxygen consumption during exercise; DFT, diastolic filling time.

Table 3 Averaged electrocardiographic and echocardiographic measurements made at baseline and at a mean follow-up for 19.4 ± 8.1 months

|	Baseline	Follow-up	95% Confidence interval	*P*-value
QRS duration (ms)	160 ± 31	120 ± 28	19 to 61	0.03
Systemic pre-ejection interval (ms)	172 ± 31	146 ± 25	0.6 to 51	NS
Pulmonary pre-ejection interval (ms)	124 ± 35	123 ± 36.3	−24 to 26	NS
Interventricular delay	49 ± 22	24 ± 15	3 to 24	NS
Duration of right ventricular systole (ms)	415 ± 43	409 ± 24	−18 to 30	NS
Septal delay (ms)	504 ± 51	391 ± 28	81 to 145	0.01
Lateral delay (ms)	401 ± 52	400 ± 28	−22.6 to 24	NS
Diastolic contraction (ms)	89 ± 29	−11 ± 15	73 to 127	0.01
Intraventricular delay (ms)	104 ± 27	14 ± 15	63 to 116	0.01
Diastolic filling time/RR (%)	38.3 ± 5.7	46.6 ± 4.3	−11.2 to −5.6	0.06

Baseline and follow-up values are means ± SD.
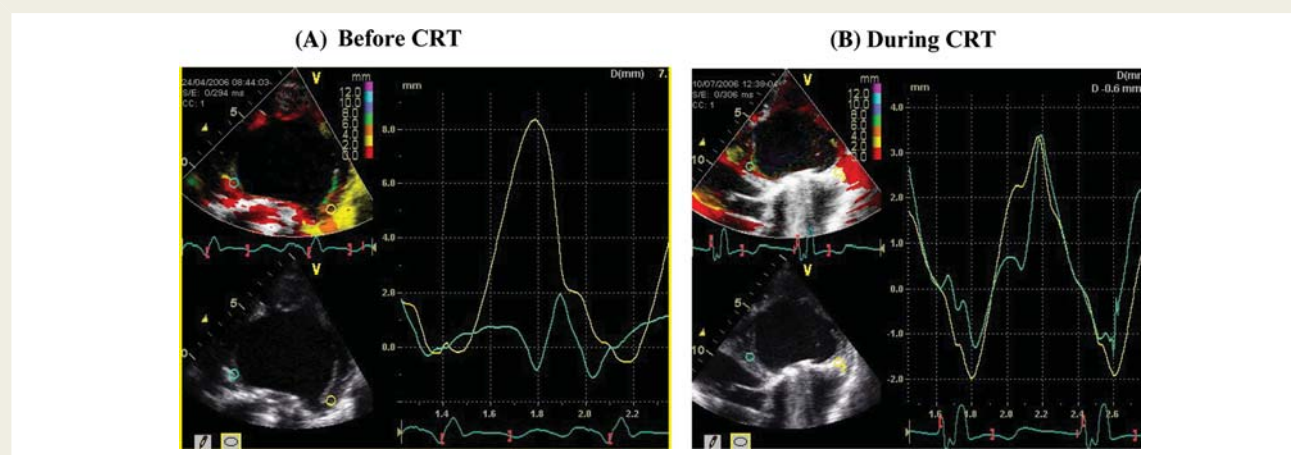
Figure 2 Tissue tracking analysis before and during CRT. Representative example of diastolic septal contraction eliminated by CRT (patient No. 7). (*A*) Before CRT. A >100 ms delay was measured between the end of contraction of the RV free wall (yellow curve), and the end of contraction of the septal wall (blue curve). (*B*) During CRT. The ends of RV free wall (yellow curve) and septal wall (blue curve) contraction are synchronous.

contraction of the VV septum, was corrected in all patients by a shortening of the septal delay. No attempt was made to optimize the VV interval during follow-up, since the resynchronization achieved with synchronous biventricular pacing appeared quite satisfactory. In general, the appropriateness of programming the VV interval is not supported by consistent long-term observations.

Cardiac resynchronization therapy also tended to improve diastolic function. Although the duration of RV systole was not significantly shortened, the RV DFT was lengthened, as has been described in patients undergoing CRT for LV systolic dysfunction and mechanical dyssynchrony.[10]

The amount of regurgitation across the systemic AV valve tended to be mitigated by CRT, though the change in regurgitation grade was not statistically significant in this small patient population. In patients undergoing standard CRT for HF due to LV systolic dysfunction, the presence of mitral regurgitation before, and its alleviation during CRT, is not known to predict a favourable

outcome. Similarly, in presence of a failing systemic RV, alleviation of tricuspid regurgitation may not be a primary therapeutic target. One of our patients with CC TGA (No. 7) had undergone tricuspid valve replacement with a mechanical prosthesis several years before CRT. Therefore, his clinical improvement was strictly attributable to the mitigation of intraventricular dyssynchrony.

Changes in QRS duration

Although CRT decreased significantly the QRS duration in our patient population, it had no significant effect on the VV delay. This is in contrast with the study by Janousek *et al.*,[7] who observed both a decrease in QRS duration and a mitigation of VV dyssynchrony. These discordant results might be due to the small number of patients included in our study. However, in the broader CRT population, QRS duration and VV delay are of limited value in the selection of candidates and prediction of response to therapy.[11] Although RV resynchronization seems to

be a promising treatment option for patients presenting with congenital heart disease and RV failure, whether the adult experience can be applied to this population, and whether RV dysfunction with a wide QRS is analogous to LV failure with a wide QRS is unclear and in need of further systematic evaluation.

Changes in functional and clinical status

The improvements in clinical status observed in our patients during follow-up are concordant with the observations made by Cowburn et al.[8] in a similar patient population. We presume that these clinical improvements were related to the improvements observed in the echocardiographic indices of cardiac mechanical function. It is likely that CRT enabled the optimization of drug therapy. Indeed, the increase or the introduction of beta-adrenergic blockers in three patients, facilitated by the haemodynamic improvement conferred by CRT, may have further improved the clinical status of some patients, who were previously intolerant of beta-adrenergic blockade. The haemodynamic improvements conferred by CRT probably also allowed the discontinuation, or decrease in doses of diuretics during CRT.

Based on the known proportion of patients who present with a failing RV, are in NYHA functional class III to IV, and have manifestations of ventricular dyssynchrony, CRT might benefit 4–9% of patients with TGA.[12] The seven CRT recipients included in this study represented 8% of the population with systemic RV followed in our medical centre. Prospective, multicenter studies are needed to: (i) better understand the correlation among RV dysfunction, cardiac dyssynchrony and functional status; and (ii) measure the long-term benefits conferred by CRT.

Leads implantation and choice of devices

Thambo et al.[13] found a deleterious effect of RV apical pacing in patients with congenital complete AV block, due to an accentuated septal-to-posterior wall delay. In our study, the septal wall was invariably delayed, including in absence of apical pacing before CRT. We hypothesized that this specific septal location of dyssynchrony was due to the RV-like architecture of the systemic ventricle. CRT eliminated that delay by stimulation of the septum with the LV lead. Although, in standard LV resynchronization, the optimal stimulation sites remain debated, the mid-lateral LV free wall is usually preferred.[14,15] Ansalone et al.[16] also reported better outcomes when the LV stimulation site was the most delayed before resynchronization. Furthermore, since apical pacing may cause ventricular dyssynchrony in some patients, the best combination of stimulation sites in CRT might be the septum and the lateral wall. Finally, in adults without congenital disease, no study has shown the alleviation of dyssynchrony and HF symptoms by relocating a RV apical lead to another RV location, whereas upgrading the pacing system from DDD pacing to biventricular stimulation has generally been effective.[17] Therefore, in previously paced patients, we abandoned the old LV lead and changed the LV stimulation site from apex to septum, with a view to resynchronize the septum and RV free wall by eliminating the late septal contraction. We found no information pertaining to placement of the LV lead in previous studies of similar patients.

All devices implanted in this study were CRT-P. Patients with CC or SC TGA are known to be at risk of atrial flutter with 1:1

AV conduction. In our study, however, the only sudden death that occurred during long-term follow-up was very likely due to a ventricular tachyarrhythmia, since the patient had been in permanent AF for several years and had undergone AV node ablation. The risk of late sudden death, in patients who have undergone Mustard or Senning repair of TGA, is estimated at 7.9 per 1000 patient-year of follow-up, and is primarily attributed to atrial reentrant tachycardia with 1:1 AV conduction to a dysfunctional systemic RV, an arrhythmia which can be treated by radiofrequency ablation.[18,19] Ventricular arrhythmias, however, are also suspected to precipitate sudden death in adults after Mustard or Senning operations.[20] The primary prevention of sudden death with implantable cardioverter defibrillator (ICD) in patients with congenital heart diseases remains controversial, as (i) the rate of device-related complications in this population is high; and (ii) there is no clear evidence that it is effective. Furthermore, in France, between 2003 and 2006 and to this day, a failing systemic RV was not a primary prevention indication for ICD implantation. It is only very recently that ICD therapy has been recommended as primary prevention for patients with non-ischaemic failing LV. However we would now recommend, for patients with a failing systemic RV and dyssynchrony, the implantation of a CRT-D, which also offers a more accurate supraventricular arrhythmia discrimination algorithm.

Study limitations

The number of patients included in this uncontrolled study was small. Furthermore, the clinical endpoints of the study were limited to: (i) changes in VO_2 max during exercise testing; and (ii) the patients' subjective perception of clinical improvement and tolerance of an optimized drug regimen. This therapy should be evaluated prospectively, and should be randomly compared with optimal medical treatment. The small number of observations limited our study of systemic AV valve function, VV delay and RV DFT, and precluded robust statistical comparisons. Finally, in absence of a widely accepted echocardiographic method of evaluation, sub-pulmonary systolic RV function and tricuspid regurgitation were assessed visually by experienced paediatric cardiologists.

Conclusions

Our observations indicate that, in patients presenting with: (i) SC or CC TGA, (ii) refractory HF deterioration; and (iii) intraventricular dyssynchrony, RV resynchronization was technically feasible and associated with improvements in cardiac mechanical function and clinical status. Dyssynchrony appeared to be located in the septum, including in absence of apical RV pacing, which may be due to the RV architecture specific to this type of congenital heart disease. In patients in need of systemic RV pacing and CRT, the septum was the preferred pacing site. As a supplement to medical treatment, CRT may effectively postpone the need for cardiac transplantation in this young patient population. Further studies are needed to examine its effects more systematically in patients with congenital heart disease and RV failure, including precise measurements of RV function, perhaps with radionuclide angiography.

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