A case series of systemic right ventricular dysfunction post atrial switch for simple D-transposition of the great arteries: The impact of beta-blockade

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BACKGROUND: Patients with atrial switch (Mustard or Senning) repair of D-transposition of the great arteries (D-TGA) are at increased risk for atrial arrhythmias, systemic right ventricular (RV) dysfunction and late mortality.

OBJECTIVES: To evaluate case series from a single-centre experience with beta-blocker use in adult, post atrial switch, simple D-TGA patients.

METHODS: The Adult Congenital Heart Disease Clinic (Halifax, Nova Scotia) database was used to identify patients with post atrial switch, simple D-TGA. Treatment effect of beta-blockade was evaluated.

RESULTS: Eight patients were treated with beta-blockers for systemic RV dysfunction (n=2), arrhythmia (n=2) or both (n=4). Median follow-up was three years, at which time seven of eight patients were still on beta-blockade. Of those patients with complete data, two of five had improved systemic ventricular dysfunction, two of four had improved tricuspid regurgitation and four of six had improved functional capacity, as determined by history or exercise testing. Beta-blockade was well tolerated in seven of eight patients without any significant clinical deterioration.

CONCLUSIONS: Beta-blockade was used infrequently in patients with a prior Mustard procedure. When beta-blockade was prescribed to patients with a prior atrial switch procedure, the drugs were well tolerated and were associated with trends toward improved symptoms, less tricuspid regurgitation and improved functional status in patients with reduced systemic RV function. These data support the need for a randomized trial of beta-blockade in patients with a previous Mustard or Senning operation and RV dysfunction.

Key Words: Beta-blockers; Congenital heart disease; Heart failure; Transposition of the great vessels

A well-established surgical approach to D-transposition of the great arteries (D-TGA) that recreates sequential circulation is the atrial baffle (Mustard or Senning) procedure. (1,2). It was performed in a clinically significant number of patients by the mid-1960s and improved the one-year survival of infants with D-TGA from approximately 10% to 90% (3). However, as a result of this procedure, the right ventricle (RV) must assume the role of the systemic pumping chamber, a function for which it was not designed.

Une série de cas de dysfonction ventriculaire droite systémique après une correction auriculaire de simple D-transposition des gros vaisseaux : Les répercussions du bêtablocage

HISTORIQUE : Les patients ayant subi une correction auriculaire (Mustard ou Senning) de D-transposition des gros vaisseaux (DTGV) sont plus vulnérables aux arythmies auriculaires, à une dysfonction ventriculaire droite (VD) systémique et à une mortalité tardive.

OBJECTIFS : Évaluer une série de cas d'après l'expérience d'un simple centre quant à l'utilisation du bêtablocage chez des patients adultes après une correction auriculaire et une simple DTGV.

MÉTHODOLOGIE : La base de données de la clinique des maladies cardiaques congénitales chez l'adulte (Halifax, Nouvelle-Écosse) a été utilisée pour repérer les patients ayant subi une correction auriculaire de simple DTGV. L'effet du traitement par bêtablocage a été évalué.

RÉSULTATS : Huit patients ont été traités par bêtablocage afin de soigner une dysfonction VD (n=2), une arythmie (n=2) ou les deux problèmes (n=4). Le suivi médian était de trois ans, moment auquel sept des huit patients étaient toujours sous bêtablocage. Sur les patients qui étaient dotés de données complètes, deux sur cinq présentaient une amélioration de la dysfonction ventriculaire systémique, deux sur quatre, une diminution de la régurgitation tricuspide et quatre sur six, une amélioration de la capacité fonctionnelle déterminée par les antécédents ou un test d'effort. Le bêtablocage était bien toléré chez sept des huit patients et ne provoquait pas de détérioration clinique significative.

CONCLUSIONS : Le bêtablocage était peu utilisé chez les patients ayant déjà subi une opération de Mustard. Lorsqu'il l'était, l'opération de Mustard était bien tolérée et s'associait à des tendances vers une diminution des symptômes et de la régurgitation fonctionnelle et une amélioration de l'état fonctionnel des patients présentant une diminution de la fonction VD systémique. Ces données étayaient le besoin d'organiser un essai aléatoire du bêtablocage chez les patients atteints d'une dysfonction VD ayant déjà subi une opération de Mustard ou de Senning.

Not surprisingly, then, there are long-term sequelae that include atrial arrhythmias, tricuspid valve regurgitation and systemic RV failure. These complications all occur at increasing rates over time, thus placing this patient population at risk for congestive heart failure and early mortality as adults (3-9).

Beta-blockers are known to improve left ventricular (LV) function, morbidity and mortality in patients with chronic LV systolic dysfunction, but patients with congenital heart disease have been excluded from these studies (10-16). While a case

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TABLE 1

Demographics of the post atrial switch, simple D-transposition of the great arteries patient population treated with beta-blockade (n=8)

Patient	Age (years)	Sex	Years from Mustard/Senning procedure	Cardiac operations, n	Additional anomalies	Concurrent medications
1	31	Male	30	5	Ventricular septal defect Sick sinus syndrome Left ventricular outflow tract obstruction	Verapamil
2	30	Male	30	2	Sick sinus syndrome	Nil
3	29	Female	28	4	Sick sinus syndrome Hypothyroid Seizure disorder	Carbamazepine Clobazam Levothyroxine
4	25	Male	24	3	Congestive heart failure Pulmonary hypertension Atrial fibrillation	Candesartan Digoxin Isosorbide dinitrate Spironolactone Furosemide Warfarin Amiodarone
5	24	Male	23	4	Atrial flutter (ablated)	Diltiazem Warfarin
6	37	Female	34	3	Multiple sclerosis	Oxybutynin Natural supplements
7	33	Female	31	3	Nil	Ramipril
8	22	Male	22	4	Congestive heart failure	Digoxin Spironolactone Lisinopril Furosemide

TABLE 2

Type, dose and indication for each post atrial switch, simple D-transposition of the great arteries patient (n=8)

Patient	Medication and dose	Indication
1	Carvedilol 25 mg bid	Supraventricular tachycardia/systemic RV dysfunction
2	Metoprolol 25 mg bid	Supraventricular tachycardia/systemic RV dysfunction
3	Sotalol 80 mg bid	Brady-tachy syndrome
4	Carvedilol 18.75 mg bid	Systemic RV dysfunction/CHF
5	Carvedilol 6.25 mg bid	Systemic RV dysfunction/atrial flutter
6	Sotalol 40 mg bid	Wide-complex tachycardia
7	Carvedilol 12.5 mg bid	Systemic RV dysfunction
8	Carvedilol 25 mg bid	Supraventricular tachycardia/systemic RV dysfunction

bid Twice daily; CHF Congestive heart failure; RV Right ventricle

report (17) of improved systemic RV function with beta-blockade has been recorded in a patient with L-TGA, no prospective studies evaluating the effect of beta-blockade on the systemic RV have been reported. The Senning or Mustard population now constitutes a cohort of patients who are at increased risk for congestive heart failure. The present report summarizes one centre's experience with eight D-TGA patients treated with beta-blockers secondary to long-term sequelae of the atrial switch procedure.

PATIENTS AND METHODS

All patients described in the present case series were followed by the Queen Elizabeth II Health Sciences Centre Adult Congenital

Heart Disease Clinic (Halifax, Nova Scotia). Computer records and case notes were used to evaluate the cardiovascular status and systemic ventricular function of each patient. Abstracted data included clinical parameters (demographics, current cardiac medications, blood pressure, heart rate, New York Heart Association [NYHA] functional class and symptomatic arrhythmias with or without a pacemaker), laboratory parameters (global RV systolic function, tricuspid regurgitation RV hypertrophy and end-diastolic RV diameter by echocardiography, all according to the American Society for Echocardiography standards [18]), RV ejection fraction (EF) by radionuclear angiography, cardiothoracic ratio (standard chest x-ray), maximum achievable oxygen consumption and metabolic equivalents, and outcomes (interventions and history of heart failure, transplant or death). Beta-blocker therapy was analyzed by comparing pretreatment with on-treatment clinical, laboratory and outcome values. Echocardiographic tapes were reviewed by two of the investigators (SJ and JH), who were blinded before analysis. Findings (RV diameter, echocardiographic grade of systemic RV systolic function and tricuspid regurgitation) were recorded as the average of the values recorded by the two observers.

RESULTS

Eight patients had been prescribed a beta-blocker (median prescription duration three years, range one to 12 years) (Table 1). Drugs, doses and indications are listed in Table 2. On initiation of therapy, the average ($\pm$ SD) heart rate decreased from 83.0 ± 8.0 beats/min to 72.0 ± 8.0 beats/min, while the average blood pressure did not change.

RV end-diastolic dimension remained relatively stable according to two-dimensional, four-chamber view echocardiographic

analyses (Table 3). Beta-blocker therapy had no adverse effects on systemic RV function or grade of tricuspid regurgitation. Four of five patients experienced either stabilized or improved systemic RV systolic function (as defined by the criteria of the American Society of Echocardiography [18]). Comparative data were not available for three patients. Likewise, the grade of tricuspid regurgitation either did not change or improved in all four patients for whom comparative data were available (Table 3). The average cardiothoracic ratio decreased ($61 \pm 3\%$ pretreatment and $56 \pm 8\%$ on treatment), while one of four patients reportedly no longer had cardiomegaly following initiation of treatment. One patient developed a new arrhythmia while on treatment (atrial fibrillation likely secondary to pre-existing congestive heart failure) and an additional patient received an elective prophylactic implantable pacemaker for procedure-related bradycardia.

Four of six patients experienced measurable improvement in functional capacity (at least one NYHA functional class) by history. One patient remained stable, while the sixth patient improved from NYHA class II to I on treatment before regressing to functional class III after developing atrial fibrillation. Although beta-blockade was discontinued in one patient (secondary to persistent fatigue and headaches), NYHA functional class by both history and stress test actually improved before the patient's medication was independently discontinued. Of the patients who underwent stress testing ($n=3$), beta-blockade was associated with a trend toward increased average maximum achievable metabolic equivalents (7.6 ± 2.2 pretreatment to 10.3 ± 2.5 during treatment). Insufficient data were available for comparison for pretreatment and treatment maximum oxygen consumption and RVEF.

Beta-blockade was well tolerated in all but one patient. No patients required pacing following initiation of therapy and no major adverse clinical events were directly attributed to beta-blocker use.

DISCUSSION

The present single-centre experience demonstrates that treatment of post-atrial switch D-TGA patients with beta-blockers is well tolerated and associated with trends toward improved measurements of clinical status.

Previous reports have indicated that a bimodal distribution of hazard of death exists after Mustard or Senning repair, with an early peak of postoperative mortality preceding a second peak of mortality during early to middle adulthood (9). By adolescence, 90% of patients with TGA develop systemic RV dysfunction, with 40% exhibiting mild, asymptomatic dysfunction (EF 40% to 60%), 40% exhibiting moderate, asymptomatic or symptomatic dysfunction (EF 20% to 40%), and 10% exhibiting severe, symptomatic dysfunction (EF less than 20%) (3,4,6-9). The clinical characteristics of our patient population are consistent with this trend. In post-atrial switch repair, simple D-TGA patients (average age 25.0 ± 5.0 years, range 18 to 37 years), systemic RV systolic dysfunction (81%) and arrhythmias (48%) were common manifestations of systemic ventricular decompensation.

Beta-blockade can reduce or attenuate the adverse myocardial response to augmented adrenergic stimulation in chronic left heart failure. Regardless of receptor specificity, beta-blockers can improve LVEF, resting hemodynamics, cardiac index, LV stroke work, mean pulmonary capillary wedge pressure and chronotropic or inotropic irregularities (10-15). In addition,

TABLE 3
A comparison of clinical variables, investigations and outcome measures before and during treatment (n=8)

Index of cardiac performance	Pretreatment	During treatment
Blood pressure, mmHg (mean $\pm$ SD)	114/73 $\pm$ 17/11	116/75 $\pm$ 17/13
Heart rate, beats/min (mean $\pm$ SD)	83.0 $\pm$ 8.0	72.1 $\pm$ 8.0
RV diameter, mm (mean $\pm$ SD)	41.5 $\pm$ 8.0	43.0 $\pm$ 4.0
(two-dimensional echo, four-chamber view)		
Systolic RV dysfunction (two-dimensional echo, four-chamber view)*		
Patient 1	Grade 2 to 3	Grade 1 to 2
Patient 4	Grade 4	Grade 4
Patient 5	Grade 1 to 2	Grade 2
Patient 6	Grade 1	Grade 2
Patient 7	Grade 2 to 3	Grade 1 to 2
Tricuspid regurgitation (two-dimensional echo, four-chamber view)		
Patient 1	Grade 2 to 3	Grade 0 to 1
Patient 5	Grade 2 to 3	Grade 2
Patient 6	Grade 0	Grade 0
Patient 7	Grade 1 to 2	Grade 1 to 2
Cardiothoracic ratio (n=4), % (mean $\pm$ SD)	61.0 $\pm$ 3.0	56.0 $\pm$ 8.0
Patients with cardiomegaly, n (computed tomography scan ratio=0.5)	4	3
Cardiac arrhythmia, n (n=7)		
Documented arrhythmia	5	6
Required pacemaker	4	5
NYHA functional class (history)		
Patient 1	I	I to II
Patient 4	IV	III
Patient 5	II	I
Patient 6	III	I
Patient 7	II	I
Patient 8	II	III†
NYHA functional class (exercise stress test)		
Patient 1	I	I
Patient 5	II	I

*Grade 1: Mild dysfunction; Grade 2: Moderate dysfunction; Grade 3: Moderate to severe dysfunction; Grade 4: Severe dysfunction; †Patient initially improved to functional class I before deteriorating to functional class III subsequent to developing atrial fibrillation. Echo Echocardiogram; NYHA New York Heart Association; RV Right ventricle

they have been demonstrated to exert antiremodelling effects that generate improvements in LV dimensions (approximately 4 mm to 6 mm at end-diastole) and function in patients with chronic heart failure (12,16). To date, comparable studies evaluating the effect of beta-blockade on the systemic RV have not been performed.

It has been postulated that conventional treatment protocols for systemic LV heart failure may be applied to systemic RV heart failure. A recent case report (17) of a single patient with L-TGA demonstrated significant improvements in RV end-diastolic volume (a reduction from 156 mL to 133 mL), RV end-systolic volume (a reduction from 127 mL to 93 mL), stroke volume (an increase from 29 mL to 40 mL) and RVEF (an increase from 19% to 30%) following initiation of beta-blocker therapy.

Although our small cohort limits interpretation, the preliminary evidence is encouraging. Beta-blocker therapy was

instituted infrequently (12%) in our patient population and was used to treat ventricular dysfunction (n=2), arrhythmia (n=2) or both (n=4). Treatment was well tolerated and trends existed toward either stabilized or improved systemic RV function (four of five patients), tricuspid valve regurgitation (four

of four patients), NYHA functional class (five of six patients) and exercise capacity (three of three). Our data therefore support the need for a prospective, randomized trial designed to evaluate the clinical effects of beta-blocker therapy in post-Mustard or Senning, simple D-TGA patients.

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