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Efficacy and Safety of Sotalol for Refractory Tachyarrhythmias in Congenital Heart Disease

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Background Sotalol is a class III antiarrhythmic agent that is highly effective for tachyarrhythmias in adults, but its efficacy in patients with congenital heart disease (CHD) remains unclear. The purpose of this study was to assess the efficacy and safety of sotalol for refractory tachyarrhythmias in patients with CHD.

Methods and Results Forty four-patients with CHD and refractory tachyarrhythmias (age, 23±12 years; follow-up period, 13±12 months) were administered sotalol orally during the period December 2002 to May 2007, resulting in complete control of tachyarrhythmias in 18 patients (41%), partial control in 15 patients (34%), and no control in 11 patients (25%). Non-pharmacological intervention (eg, surgery, pacemaker implantation, catheter ablation) was performed in 9 patients and resulted in an augmented response to sotalol in 6 patients. Tachyarrhythmia combined with atrial fibrillation was a risk factor for treatment failure with sotalol (odds ratio, 18.3; 95% confidence interval, 1.8–189.6; p=0.0053).

Conclusion Sotalol is partially or completely effective for refractory tachyarrhythmias in patients with CHD, and non-pharmacological interventions improve the efficacy of sotalol. This multimodal approach should be considered in patients with refractory tachyarrhythmias and CHD. (*Circ J* 2008; **72:** 1998–2003)

Key Words: Congenital heart disease (CHD); Sotalol; Tachyarrhythmia

Class III antiarrhythmic agents exert their strong antiarrhythmic effect on tachyarrhythmias by blocking potassium channels, thereby prolonging the myocardial cells' action potential duration and refractoriness. Furthermore, these agents do not affect cardiac output and are thus safe to use in patients with heart failure. Although amiodarone is more effective than sotalol in patients with atrial fibrillation (AF), ventricular tachycardia (VT) or congestive heart failure[1–4] sotalol has the advantages of simpler pharmacokinetics and fewer side-effects[5] Sotalol is used as first- or second-line therapy for many types of tachycardia, even in patients with structural heart disease. However, according to the Japanese Circulation Society (JCS) guidelines for drug treatment of arrhythmias, sotalol is not the treatment of choice for patients with severe cardiac dysfunction[6]

In patients with congenital heart disease (CHD), tachyarrhythmias are often refractory to medical treatment and can result in sudden death, particularly in those with inoperable, cyanotic CHD, and those with single-ventricle physiology or complicated severe cardiac dysfunction. There is a relative scarcity of studies that investigate the efficacy and safety of sotalol in patients with CHD, especially in the Japanese population.

The goal of the present study was to investigate the efficacy and safety of sotalol in patients with CHD and refractory tachyarrhythmias.

Methods

Patients

From December 2002 to May 2007, 44 patients (21 females 23 male) with CHD were given oral sotalol at the National Cardiovascular Center in Japan and the clinical course of the tachyarrhythmias and efficacy of sotalol was followed retrospectively. Diagnoses of CHD consisted of univentricular heart (including hypoplastic LV or RV) in 10, tetralogy of Fallot in 12, transposition of the great arteries in 5, tricuspid stenosis or atresia in 5, corrected transposition of the great arteries in 3, Ebstein's anomaly in 3, congenital mitral valve insufficiency in 2, pulmonary atresia in 1, ventricular septal defect in 1, aortic valve stenosis and insufficiency in 1, and total anomalous pulmonary venous connection in 1.

Diagnosis of the tachyarrhythmias was based on surface ECG, 24-h ambulatory Holter monitoring or treadmill exercise tolerance test. Nonsustained tachyarrhythmias of more than 3 beats were included as the targets of treatment in this study.

Assessment of the Efficacy of Sotalol

Efficacy of antiarrhythmic therapy was judged according to clinical symptoms, follow-up 24-h ambulatory Holter monitoring, or treadmill excise tolerance testing. Complete control was defined as no recurrence of tachyarrhythmias after administration of sotalol. Partial control was defined as improvement in clinical symptoms, decreasing frequency and prolongation of cycle length, or shorter duration of

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Table 1 Characteristics of Patients

	Total (n=44)	Complete control (n=18)	Partial control (n=15)	Failure (n=11)	Overall p value
Age at administration (years)	23±12	18±10	26±10	24±13	NS
Female gender (n)	21 (48%)	12 (67%)	5 (33%)	4 (36%)	NS
Follow-up period (months)	13±12	13±10	13±9	13±17	NS
Type of tachyarrhythmia					
SVT	27 (61%)	14 (52%)	6 (22%)	7 (26%)	NS
VT	8 (18%)	2 (25%)	5 (63%)	1 (13%)	
SVT + VT	9 (20%)	2 (22%)	4 (44%)	3 (33%)	
Only supraventricular reentrant tachyarrhythmia	14 (32%)	8 (44%)	3 (20%)	3 (27%)	NS
≥2 types of tachyarrhythmia	15 (34%)	5 (28%)	5 (33%)	5 (45%)	NS
Combined with AF	5 (11%)	0	1 (7%)	4 (36%)	0.0092
Previous antiarrhythmogenic drugs#	1.6±1.1	1.4±1.3	1.8±0.9	1.5±1.0	NS
β-blocker at administration of sotalol (n)	14 (32%)	3 (17%)	9 (60%)	2 (18%)	0.0166
Surgical history					
Surgery#	2.0±1.4	2.0±1.1	2.0±1.2	2.2±2.0	NS
No corrective surgery (n)	5 (11%)	2 (11%)	1 (7%)	2 (18%)	NS
Interval after corrective surgery (years)	12±11	10±9	16±13	8±9	NS
ECG					
QRS duration (ms)	123±42	122±41	125±42	124±48	NS
QRS ≥160 ms (n)	14 (32%)	5 (28%)	6 (40%)	3 (27%)	NS
Pacemaker at administration of sotalol (n)	5 (11%)	2 (11%)	3 (20%)	0	NS
Single-ventricle physiology (n)	17 (39%)	8 (44%)	4 (27%)	5 (45%)	NS
Isomerism heart (n)	6 (14%)	2 (11%)	2 (13%)	2 (18%)	NS
NYHA ≥III (n)	5 (11%)	0	2 (13%)	3 (11%)	0.0391
Natriuretic peptide					
BNP (pg/ml)	104±105	96±80	116±143	100±80	NS
hANP (pg/ml)	89±100	106±134	67±63	94±71	NS
BNP ≥200 pg/ml (n)	6/42 (14%)	2 (11%)	3 (20%)	1 (9%)	NS

#No. of drugs administered or no. of procedures.
SVT, supraventricular tachycardia; VT, ventricular tachycardia; AF, atrial fibrillation; NYHA, New York Heart Association; BNP, B-type natriuretic peptide; hANP, human atrial natriuretic peptide.

tachyarrhythmias. Failure was defined as discontinuation of sotalol secondary to adverse effects or the inability of therapy to modulate any parameters of the tachyarrhythmia.

Changes in heart rate (HR), QRS duration, QTc and the levels of B-type natriuretic peptide/human atrial natriuretic peptide (BNP/hANP) were compared before and after administration of sotalol. Patients with a pacemaker or those receiving a β-blocker with a different status before and after sotalol administration were excluded from HR analysis. Patients receiving other antiarrhythmic agents (class I or IV) were excluded from analysis of QRS duration and QTc, and patients who were started on sotalol perioperatively were excluded from analysis of BNP/hANP.

The following possible predictors of the effectiveness of sotalol were explored: age at administration, sex, follow-up period, diagnosis of tachyarrhythmia (supraventricular reentrant tachyarrhythmia only, presence of more than 2 types of tachyarrhythmia, or tachyarrhythmia combined with AF), β-blocker therapy at time of administration, surgical history (number of previous surgeries, no corrective surgery, interval after corrective surgery), QRS duration, pacemaker, single-ventricle physiology, isomerism heart, clinical status (New York Heart Association (NYHA) ≥III), and BNP level ≥200 pg/ml.

Statistical Analysis

Values are shown as mean±SD unless otherwise specified. Comparisons were made with the 2-tailed unpaired Student's t-test, 1-way ANOVA, χ^2, or Fisher's exact test, where appropriate. The relationship between dose and HR was analyzed using linear regression. A p-value <0.05 was considered statistically significant.

Results

Rhythm Determination and Indications for Class III Agents

Rhythms were supraventricular tachycardia (SVT) in 27 patients (61%), VT in 8 (18%), and complicated SVT/VT in 9 (20%). SVT consisted of intra-atrial reentrant tachycardia (IART) in 14 patients, atrial tachycardia (AT) in 8, atrioventricular reentrant tachycardia in 1, complicated IART/AT in 2, complicated IART/AF in 1, and complicated IART/AF/junctional tachycardia (JT) in 1. VT consisted of nonsustained VT (NSVT) in 6 patients, sustained VT in 1, and ventricular fibrillation in 1. In the patients with complicated SVT/VT, all had NSVT, and SVT consisted of IART in 3 patients, AT in 1, IART/AT in 1, IART/AT in 3, and undiagnosed narrow QRS tachycardia in 1.

The indication for sotalol treatment was uncontrollable tachyarrhythmia despite the use of 1 or more antiarrhythmic medications in 31 patients, perioperative tachyarrhythmias in 6 patients, hemodynamically overloaded hearts in 5 patients, life-threatening tachyarrhythmia after ICD implantation in 1 patient, and tachyarrhythmia during pregnancy in 1 patient.

Characteristics of the Patients (Table 1)

Mean age of patients receiving sotalol was 23±12 years (0.1–42 years) with a follow-up period of 13±12 months. The number of previous antiarrhythmic drugs was 2±1. Study patients with CHD included those who had not undergone corrective surgery (n=5; 11%), those with single-ventricle physiology (n=17; 39%), those with isomerism heart (n=6; 14%), those with NYHA class III or IV (n=5; 11%), those with high BNP level (≥200 pg/ml: 6/42 patients, 14%),

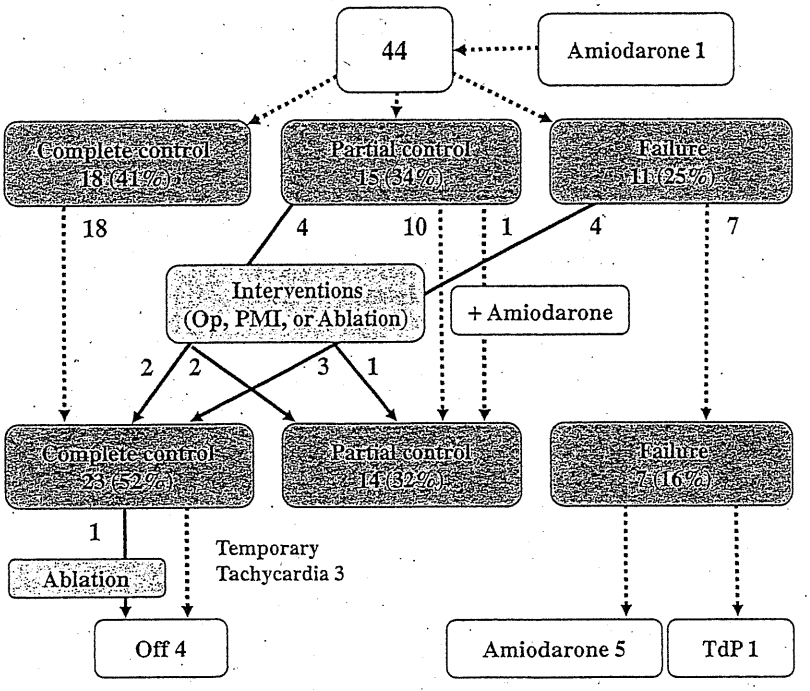

Fig 1. Efficacy of sotalol. The solid line shows cases with non-pharmacological interventions (surgical operation (Op), pacemaker implantation (PMI) or catheter ablation) and the dotted line indicates those without interventions. Sotalol was effective in 33 of 44 patients (75%) (complete control, n=18 (41%); partial control, n=15 (34%)). Non-pharmacological interventions improved the efficacy of sotalol. Ultimately, sotalol was effective in 84% of 44 patients (complete control, n=23 (52%); partial control, n=14 (32%)) and was ineffective in 16%. Tdp, torsades de pointes.

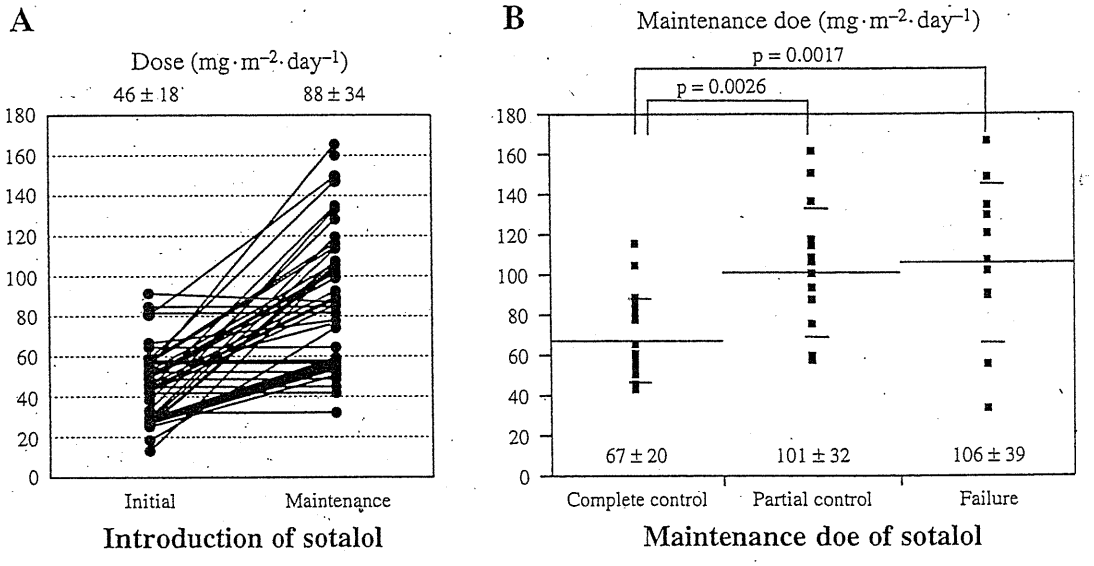

Fig 2. Dosing. (A) Sotalol was initially administered at a relatively low dose (46 mg·m^{-2}·day^{-1} divided into 3 doses for infants, and 2 doses for children and adults) and was increased gradually after observing its effect on tachyarrhythmias and whether there were any side-effects. (B) Maintenance dose of sotalol was lower in patients with complete control than in those with partial control or failure.

and those with wide QRS interval (≥160 ms; 14, 32%).

In addition to sotalol, β-blockers were administered in 14 patients, digoxin in 8, verapamil in 1, aprindine in 1, and flecainide in 1.

Efficacy of Sotalol (Fig 1)

One of the patients had previously received amiodarone, but it was ineffective. Complete control of tachyarrhythmias was achieved in 18 patients (41%), partial control was achieved in 15 (34%), and failure occurred in 11 (25%) in response to therapy with sotalol alone. Eight patients underwent non-pharmacological interventions (eg, surgical intervention, pacemaker implantation, or catheter ablation), which resulted in improved efficacy of sotalol in 6 patients. The addition of amiodarone to sotalol improved efficacy in 1 patient. Thus, the final efficacy of sotalol was complete control in 23 patients (52%), partial control in 14 (32%) and failure in 7 (16%). Four patients with complete control discontinued sotalol during follow-up; 5 of 7 patients with failure on sotalol were transitioned to amiodarone, with 1 subsequent death because of torsades de pointes (TdP), and 1 patient had persistent AT and AF.

Dosage

Sotalol was started with a relatively low initial dose (46 mg·m^{-2}·day^{-1} divided into 3 doses for infants, and 2

Table 2 Effects of Sotalol on HR, BP, ECG and BNP/hANP

	n	Before	After	Δ
Holter ECG				
HR min (beats/min)	16	56±15	51±17	−6†
HR max (beats/min)	14	113±27	97±23	−16‡
HR mean (beats/min)	15	76±15	67±18	−9‡
Treadmill				
HR rest (beats/min)	7	78±19	67±10	−11
HR max (beats/min)	7	157±27	132±27	−24‡
BP rest (mmHg)	7	100±15	106±15	−6
BP max (mmHg)	6	157±31	138±20	−19
ECG				
QRS in II (ms)	24	123±38	125±36	2
QTc in V5 (ms)	24	427±29	445±40	18‡
BNP (pg/ml)	32	98±105	102±110	5
hANP (pg/ml)	21	96±117	101±158	5

†$p<0.001$; ‡$p<0.01$.
HR, heart rate; BP, blood pressure. See Table 1 for other abbreviations.

Table 3 Interventions for Tachyarrhythmias

Patient no.	Diagnosis	Previous operation	Tachyarrhythmia	Intervention operation	PMI	ABL	Effectiveness	NYHA
1	TOF, PA	ICR	IART, NSVT	● re-RVOTR, PVR, RA-Maze	●	●	P→P	III→II
2	TOF	ICR	IART, NSVT	● PVR		●	F→P	II→II
3	Ebstein	TVR	IART	● re-TVR, Maze			P→C	II→II
4	UVH	Fontan	IART, AF, JT		●		F→C	II→II
5	TGA	Mustard	IART		●		P→C	II→II
6	PA	TCPC conversion	IART		●		F→C	II→II
7	cTGA	DSO	IART, NSVT		●		P→P	III→II
8	TOF	ICR	IART			●	F→C	II→II
9	TOF	ICR	IART			●	C→off	I→I

PMI, pacemaker implantation; ABL, catheter ablation; TOF, tetralogy of Fallot; PA, pulmonary atresia; ICR, intracardiac repair; IART, intra-atrial reentrant tachycardia; NSVT, nonsustained VT; RVOTR, right ventricular outflow tract reconstruction; PVR, pulmonary valve replacement; P, partial control; F, failure; Ebstein, Ebstein's anomaly; TVR, tricuspid valve replacement; C, complete control; UVH, univentricular heart; TGA, transposition of the great arteries; TCPC, total cavopulmonary connection; cTGA, corrected transposition of the great arteries; DSO, double switch operation. See Table 1 for other abbreviations.

doses for children and adults) with the dose increases every week as needed after recording clinical symptoms, HR, and QT interval (mean maintenance dose: 88 $mg \cdot m^{-2} \cdot day^{-1}$) (Fig 2A). The maintenance dose was lower in patients with complete control than in patients with partial control or failure (Fig 2B).

Effects on HR, ECG and BNP/hANP

Sotalol decreased all HR parameters on Holter monitoring and maximal HR and on treadmill excise tolerance testing, and prolonged QTc (Table 2). Linear regression showed a significant relationship between the dose of sotalol and minimum HR on Holter monitoring ($r^2=0.33$, $p=0.02$). Sotalol had no significant influence on other parameters, including BNP/hANP levels. Changes in HR and QTc after sotalol did not differ among the patients with complete control, partial control or failure.

Predictors of Effectiveness of Sotalol

Characteristics of the patients with complete control, partial control and failure are shown in Table 1. Differences in these 3 groups were observed for tachyarrhythmias combined with AF, β-blocker therapy at time of administration, and NYHA ≥III. Among these parameters, there were no valuable predictors for patients with complete control. Tachyarrhythmia combined with AF was a predictor for treatment failure in response to sotalol (odds ratio, 18.3; 95% confidence interval, 1.8–189.6; $p=0.0053$). Four patients with a tachyarrhythmia combined with AF did not respond to sotalol; after sotalol administration, IART/AF occurred in 2 patients, AF/NSVT in 1, and NSVT/TdP in 1.

Non-Pharmacological Interventions

Nine patients underwent non-pharmacological intervention combined with sotalol therapy (Table 3). Surgical procedures were performed in 3 patients, with the Maze procedure performed in 2 of them. The Maze procedure was unable to be performed in 1 patient secondary to extremely large right atrium and ventricle. Pacemaker implantation was performed in 5 patients, and catheter ablation was performed in 4 patients.

Non-pharmacological interventions improved the efficacy of sotalol in 6 patients and enabled withdrawal of sotalol in 1 patient.

Adverse Effects

One patient died of TdP during administration of sotalol. Although we strongly recommended surgical repair for severe congenital mitral valve insufficiency for this 34-year-old patient with Williams syndrome, severe mental retardation and renal insufficiency (serum creatinine 1.2 mg/dl), his family declined. Sotalol (240 mg, 166 mg/m^2) was administered for polymorphic NSVT, AT and AF. This patient died 4 months after initiation of sotalol administration and 3 weeks after the last increase in drug dose. The QTc interval was 470 ms at 2 weeks before his death.

Two patients complained of fatigue with sotalol, and sotalol therapy was ceased in 1 of them. Five patients re-

Table 4 Published Reports of the Efficacy of Sotalol and Amiodarone in Pediatric Patients

Authors	Year	n	Age (years)	CHD	Tachy-arrhythmias	Follow-up (years)	Dose ($mg \cdot m^{-2} \cdot day^{-1}$)	Complete control	Partial control	Failure	Side-effects#
Maragnes et al[7]	1992	66	8.7 (0–24)	28 (42%)	SVT, VT	1.1 (0.2–5)	135	62%	17%	21%	5%
Tanel et al[8]	1995	45	8.1 (0–26)	13 (29%)	SVT, VT	1.3 (0–4.7)	116±52	52%	28%	20%	9%
Pfammatter et al[9]	1995	71	7.3 (0–20)	33 (46%)	SVT, VT	–	101±45	55%	31%	14%	8%
Beaufort-Krol et al[10]	1997	26	7.5	26 (100%)	SVT	–	4.0±1.6 ($mg \cdot kg^{-1} \cdot day^{-1}$)	Recurrence-free interval of 2 years was 81%			0%

#Side-effect requiring discontinuation of sotalol.
CHD, congenital heart disease. See Table 1 for other abbreviations.

ceiving sotalol required pacemaker implantation. Because of the inclusion of patients with latent conduction disturbance caused by unusual anatomy and hemodynamics, it was difficult to determine whether the bradycardia in these 5 patients could be attributed to the adverse effect of sotalol.

Discussion

The present study investigated the efficacy of sotalol in patients with CHD and refractory tachyarrhythmias. Antiarrhythmic agents are typically not efficacious in patients with complicated CHD, particularly those with multiple anomalies and hemodynamically overloaded hearts, and these patients sometimes require both surgical and medical treatment in order to reduce arrhythmogenicity. Indeed, 9 patients in the present study had combination therapy of sotalol and non-pharmacological interventions, which resulted in improved pharmacologic efficacy in 6 patients, and another patient was able to discontinue treatment with sotalol. Thus, non-pharmacological interventions based on the hemodynamic evaluation should be considered for patients with refractory tachyarrhythmias.

The efficacy of sotalol in pediatric populations has been investigated, including in those with structurally normal hearts[7–10] (Table 4). Although the efficacy of sotalol in the present study of a Japanese population was similar to that in previous reports, the maintenance dose was relatively lower in the present study. It is likely that the optimal dose of sotalol differs between patients of different ethnicities. For example, a twice-daily sotalol dose of 120 mg provided the most favorable benefit in a study of adult Caucasian, Black, and Hispanic patients,[11] whereas another study of Japanese patients reported that the optimal was 80 mg and that 40 mg was the recommended initial dose.[12] This is supported by the present patients achieving partial or complete control with a comparatively lower maintenance dose. Furthermore, the patients with complete control required a lower maintenance dose than the patients with partial control or failure. Although there were no predictors for complete control, some patients had a good response to a low dose of sotalol.

In the present study, tachyarrhythmia combined with AF was a predictor for failure to respond to sotalol. The efficacy of sotalol for maintaining sinus rhythm in patients with AF is relatively low in studies of adults[1–3,13] However, the mechanism of AF likely differs in patients with and without CHD, indicated by the fact that all patients with AF in the present study had complications with other tachyarrhythmias, such as IART, JT and/or VT. Tachyarrhythmia combined with AF in CHD implies progression of structural and electrophysiologic remodeling caused by impaired hemodynamics. In our study, 4 patients with tachyarrhythmia combined with AF failed to respond to treatment with sotalol. These patients experienced not only AF, but also IART, NSVT or TdP after administration of sotalol. Thus, sotalol may be ineffective in patients with advanced cardiac remodeling.

The dose-related adverse effects of sotalol include bradycardia mediated by β-adrenergic blockade, QT prolongation with reverse use dependence, and proarrhythmia with risk of TdP.[5,12,14] In this study, 2 patients had to discontinue sotalol secondary to adverse effects (TdP and fatigue). However, sotalol did not affect BNP/hANP levels, even in those with complicated CHD and severe heart failure. This favorable safety profile may be related to our starting sotalol at a lower dose and maintaining it at a relatively low dose, compared with other trials of sotalol.

One patient with severe congestive heart failure and mitral insufficiency, multifocal tachyarrhythmias, and renal failure died secondary to TdP. TdP occurs in 2.4% of those receiving sotalol, mostly within the first week of initial treatment or after dose adjustment.[5,15] Risk factors for TdP include female gender, sustained VT/ventricular fibrillation, history of congestive heart failure, sotalol dose >320 mg/day, and elevated baseline serum creatinine.[5] In this case, TdP occurred more than 1 week after the last increase in the sotalol dose. The causation is unclear and in retrospect, amiodarone, with its lower reverse use-dependence and lower effects on renal function, would have been a better choice for this patient.

Among the class III agents, amiodarone is more effective than sotalol in pediatric patients.[16–20] However, it can produce pulmonary toxicity and disturbances of thyroid function.[5,14] Because amiodarone is a highly lipophilic compound and affects multiple organ systems during long-term administration,[5] its use should be considered more carefully in younger patients who are not expected to reach the endpoint of administration. Compared with amiodarone, sotalol has the advantage of relatively simple pharmacokinetics. Peak plasma concentrations occur 2–4 h after oral dosing, and most adverse effects occur within the first week after initiation of treatment.[5] Therefore, sotalol is useful even for patients with perioperative hemodynamic instability. We use sotalol as the first-line therapy for refractory tachyarrhythmias in patients with CHD, including in the perioperative setting, whereas amiodarone is used as first-line therapy for patients with severe heart failure or a history of syncope or near-sudden death.

Conclusion

In the present study, sotalol was partially or completely effective for the treatment of refractory tachyarrhythmias in patients with CHD. Further, this therapy was well tolerated,

even in patients with severe heart disease (eg, inoperable heat disease, cyanotic heart disease, single-ventricle physiology, and NYHA class III or IV), and non-pharmacological interventions in these patient improved the response to sotalol.

These findings suggest that sotalol is useful and effective for decreasing the frequency of tachyarrhythmias in patients with CHD, including those with multiple anomalies and with hemodynamically overloaded hearts. The combination of non-pharmacological interventions and sotalol should be considered for the treatment of refractory tachyarrhythmias in patients with CHD. Further study in larger patient populations and with longer follow-up would be of benefit to validate these results.

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Morphologic Spectrum of Ventriculoarterial Connection in Hearts With Double Inlet Left Ventricle: Implications for Surgical Procedures

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Background. This study was conducted to determine a morphologic spectrum of ventriculoarterial connection in double inlet left ventricle and implications for surgical procedures.

Methods. Examined were 54 autopsied heart specimens and 43 consecutive clinical patients.

Results. The hypoplastic and incomplete morphologic right ventricle was located leftward to the dominant ventricle in 62 and adjacent to the right atrium in 35. Common patterns were seen in 46 of 62 (74%) with the right ventricle leftward (discordant ventriculoarterial connection with the aorta left-anteriorly located ["SLL" type]) and in 28 of 35 (80%) with the right ventricle rightward (either the normally connected great arteries in 13 or discordant connections with the aorta right-anteriorly located in 15). In the remaining 23 hearts, the great arteries were unusually oriented in 7, the outlet septum was malaligned in 9, or the pulmonary trunk was atretic in 7. In those with malalignment, the ventriculoarterial connections were double outlet from the right ventricle, from the left ventricle, or were transitional with overriding of one of the great arteries. In the clinical series, 19 of 35 patients (54%) in whom the aorta arose from the morphologically right ventricle underwent either myectomy to enlarge the interventricular communication or a Damus-Kaye-Stansel anastomosis was fashioned to treat existing or potential subaortic stenosis. Only 1 of 8 patients with the aorta arising from the dominant ventricle needed similar surgical procedures.

Conclusions. Ventriculoarterial connection in double inlet left ventricle demonstrated a morphologic spectrum and needs precise recognition to provide an unobstructed ventricular outflow after operation.

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In the setting of double inlet left ventricle, discordant ventriculoarterial connection is commonly seen in hearts with a hypoplastic and incomplete morphologically right ventricle on the left side (the so-called SLL type) [1–3], whereas a concordant ventriculoarterial connection, which is a vital element for the so-called Holmes heart, is less common [4, 5]. A small proportion of hearts with double inlet left ventricle have some other manner of ventriculoarterial connections, such as double outlet from the right or the left ventricle [6, 7]. Accordingly, we investigated a combined series of hearts with this entity, in postmortem specimens and in patients, focusing on ventriculoarterial connections to determine precisely the morphologic spectrum and to consider implications for options available for surgical procedures.

Material and Methods

This retrospective study was approved by the Institutional Ethics Committee, and individual patient consents were waived.

We examined 54 autopsied heart specimens of double inlet left ventricle. Another consecutive series of 43 clinical patients were assessed on the basis of imaging as well as direct inspection during heart operations. All patients underwent an intracardiac operation, and none were included in the autopsied series. The type of definitive repair was ventricular septation in 22 and the Fontan type procedure in 19. One patient remained with the bidirectional Glenn physiology, and another patient with coarctation of the aorta underwent the Norwood type procedure.

In total, 96 had the usual atrial arrangement, and only 1 clinical patient possessed its mirror imagery. This exceptional case was described as seen in a mirror so that we could correlate it with the other cases. The incomplete and hypoplastic morphologically right ventricle was located anteriorly and to the left of the dominant left ventricle in 62, but rightward and adjacent to the right atrium in 35.

Results

The morphologic features around the ventriculoarterial connection are summarized in Table 1.

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Table 1. Summary of Morphologic Features Around the Ventriculoarterial Connections

Feature	RV Leftwards	RV Rightwards
Ventriculoarterial connection[a]		
Concordant	2	13
Discordant	51	16
Double outlet RV	1	3
Aorta from RV/pulmonary atresia	6	1
Double outlet LV	2	1
Aorta from LV/pulmonary atresia	...	1
Infundibular morphology		
Subpulmonary	2	13
Subaortic	58	17
Subpulmonary & subaortic	1	3
Markedly attenuated	1	2
Aortic valve in relation to pulmonary valve		
Right posterior	2	14
Right anterior	2	17
Right side-by-side	2	3
Left anterior	54	...
Left side-by-side	2	1
Arterial trunks		
Spiraling	2	14
Parallel	60	21

[a] For overriding of the aortic or the pulmonary valve, the so-called 50% rule was applied.

LV = morphologic left ventricle; RV = morphologic right ventricle.

Common Types

Of 62 with the right ventricle leftwards, 46 (74%) had the SLL type, in which the left-anteriorly located ascending aorta originated entirely from the morphologically right ventricle with the pulmonary trunk (right posterior) entirely from the dominant left ventricle (Fig 1). Of 35 with the right ventricle rightwards, 13 (37%) had the Holmes heart, with the normally related great arteries with concordant ventriculoarterial connection, and 15 (43%) had discordant ventriculoarterial connection with the aorta located right anteriorly to the pulmonary trunk (Fig 2).

Atypical Patterns in Hearts With the Right Ventricle Leftwards

Four (6%) had discordant ventriculoarterial connections but with unusual aortopulmonary orientations (Fig 1); the aorta was to the left of the pulmonary trunk in a side-by-side fashion in 2 or was right-anteriorly located in 2. The outlet septum in these 4 hearts was in alignment with the muscular ventricular septum; in another 4, the outlet septum was malaligned (posteriorly oriented in relation to the muscular ventricular septum). Because of that, the aorta was overriding the left ventricle by 25% in 2, by 50% in 1, or exclusively arising from the left ventricle in the remaining 1. In these hearts the aorta was anterior or left anterior to the pulmonary trunk. No heart had a concordant ventriculoarterial connection when the aorta was located anteriorly to the pulmonary trunk; this particular situation is known as a part of the features that are seen in the so-called anatomically corrected malposition.

In one heart in which the aorta was located to the right and side-by-side to the pulmonary trunk, both great arteries arose entirely from the incomplete and hypoplastic morphologic right ventricle. The outlet septum was unequivocally malaligned with the muscular ventricular septum. In another 2 with the aorta normally orientated relative to the pulmonary trunk, the ventriculoarterial connection was concordant, and there was no malalignment of the outlet septum. These 2 hearts had a regular spiraling arrangement of the great arteries.

In the remaining 6 hearts (10%), there was pulmonary atresia, with the aorta arising entirely from the morphologic right ventricle, including 1 with an imperforate pulmonary valve (Fig 3). The remnant of the pulmonary trunk suggested a left anterior orientation of the aorta in 5 and right side-by-side in 1.

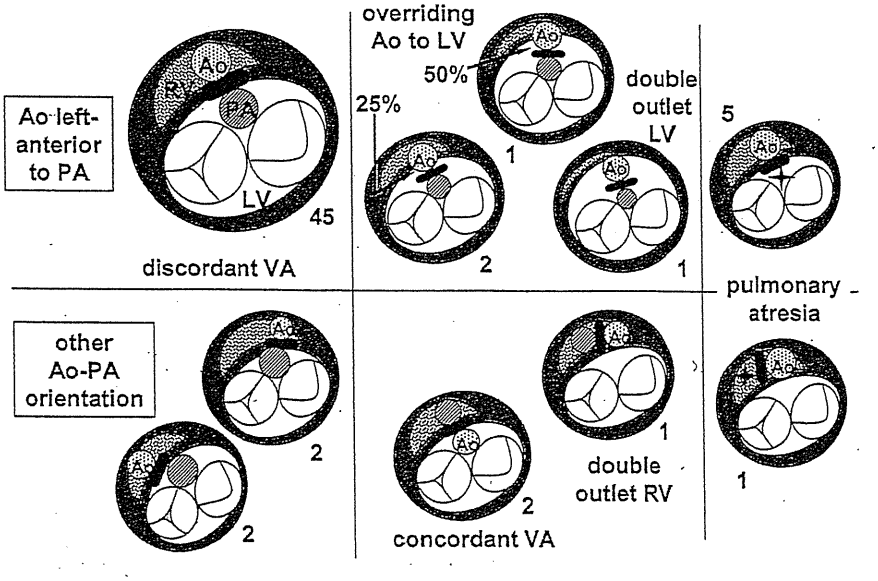

Fig 1. Diagrams of ventriculoarterial connections in patients and specimens with double inlet left ventricle with the right ventricle leftwards in relation to the dominant left ventricle. The schemas are drawn as seen from the top. The numbers of examples are shown adjacent to each schema. Percentages indicate degree of overriding of the aorta. (Ao = aorta; LV = morphologic left ventricle; PA = pulmonary arterial trunk; RV = morphologic right ventricle; VA = ventriculoarterial connection.)

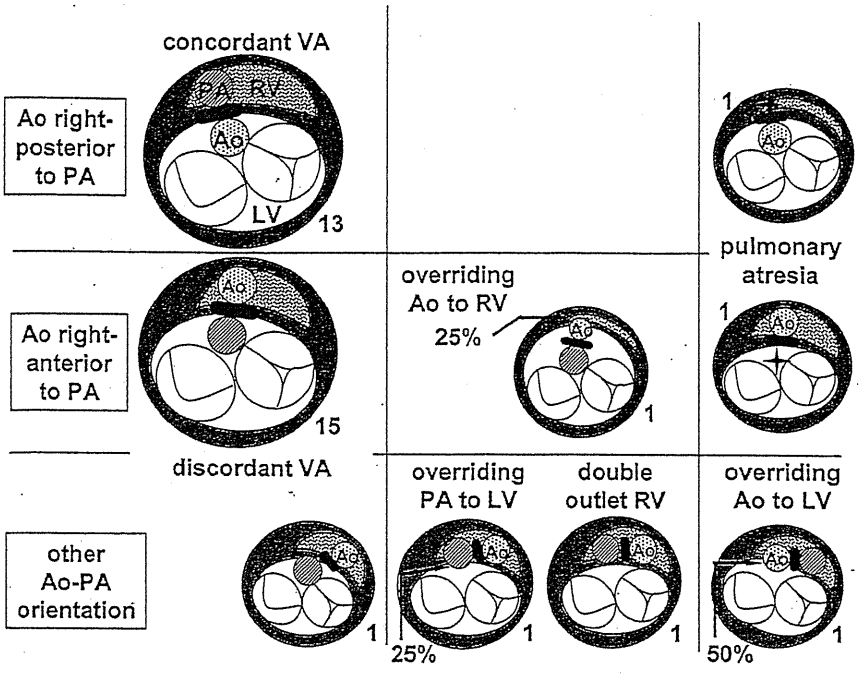

Fig 2. Diagrams of ventriculoarterial connections in patients and specimens with double inlet left ventricle with the right ventricle rightwards and adjacent to the right atrium. The schemas are drawn as seen from the top. The numbers of examples are shown adjacent to each schema. Percentages indicate degree of overriding of either the aorta or the pulmonary trunk. (Ao = aorta; PA = pulmonary arterial trunk; RV = morphologic right ventricle; LV = morphologic left ventricle; VA = ventriculoarterial connection.)

Atypical Patterns in Hearts With the Right Ventricle Rightwards

The aorta was to the right of the pulmonary trunk in a side-by-side fashion in 3 hearts (Fig 2, lower row). Although the aorta originated entirely from the right ventricle, the pulmonary trunk was entirely from the right ventricle (double outlet right ventricle; Fig 3), with 25% overriding the dominant left ventricle or entirely from the left ventricle (discordant ventriculoarterial connection).

In another example, the aorta was left and side-by-side to the pulmonary trunk, and 50% overriding to the dominant left ventricle with the pulmonary trunk arising from the right ventricle. In one case with right-anterior aorta, the aorta was overriding by 25% to the right-anterior right ventricle (Fig 2, in the middle pane).

Two hearts had an atretic pulmonary trunk, with the aorta arising from either the right or the left ventricle. The remnant of the pulmonary trunk indicated the potential orientation of the great arteries as seen in the

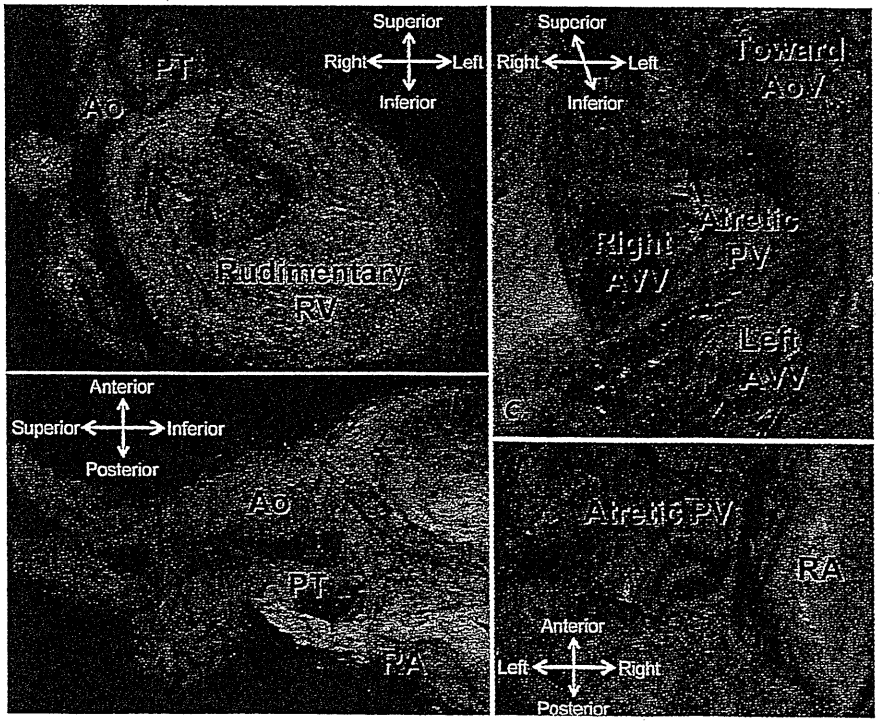

Fig 3. (a) An example of both great arteries arising from the right-sided morphologic right ventricle. The ventricular septal defect is large, and the outlet septum is oriented perpendicular to the muscular ventricular septum. Panels b, c, and d show examples of unusual ventriculoarterial connections; the aorta arising from the morphologically right ventricle and the pulmonary pathway having membranous atresia. (b) The aorta was anterior to the pulmonary trunk, and the arterial trunks had a parallel arrangement. (c) From the dominant morphologic left ventricle, the imperforate pulmonary valve was seen in relation to the crest of the muscular ventricular septum, while the forceps through the aortic valve indicated that the aortic valvar orifice exclusively originated from the morphologic right ventricle. The outlet septum was markedly attenuated. (d) This view from the pulmonary trunk revealed an imperforate pulmonary valve. (Ao = aorta; AoV = aortic valve; AVV = atrioventricular valve; PT = pulmonary arterial trunk; PV = pulmonary valve; RA = right atrium; RV = morphologic right ventricle.)

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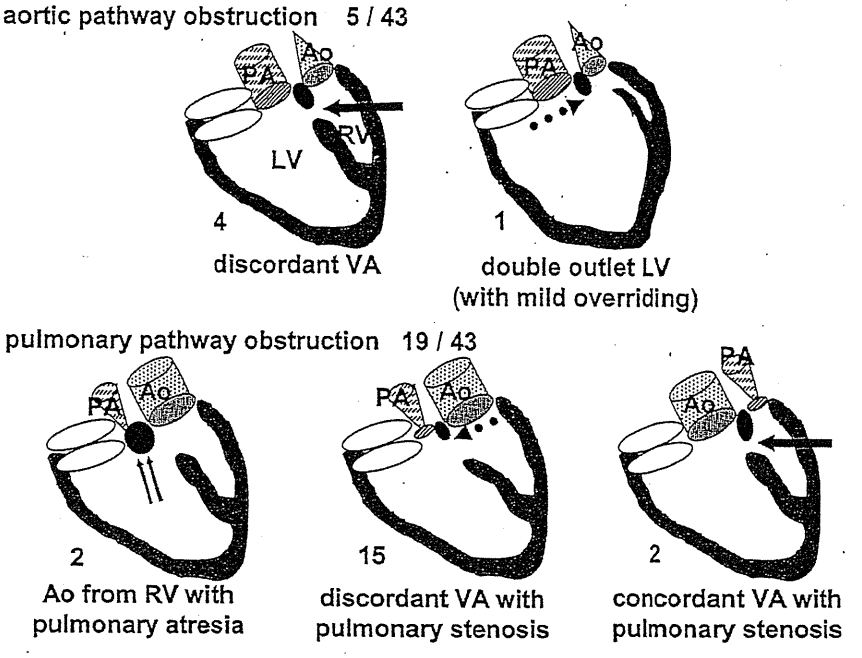

Fig 4. Diagrams of obstructions across the aortic or pulmonary pathway in clinical patients. A solitary arrow indicates a restrictive interventricular communication. A broken arrow indicates deviation of the outlet septum. A dual arrow shows a markedly deviated and substantially formed outlet septum. Aortic pathway obstruction includes coarctation of the aorta, interruption of the aortic arch, or subaortic stenosis. (Ao = aorta, LV = morphologic left ventricle; PA = pulmonary arterial trunk; RV = morphologic right ventricle; VA = ventriculoarterial connection.)

common patterns for hearts with the right ventricle rightwards.

Ventricular Outflow Tracts in the Clinical Series

Obstruction of the aortic arch coexisted in 5 (coarctation in 4 and interruption in 1) of 43 clinical patients (12%). In 4 the right ventricle was leftwards and there was a discordant ventriculoarterial connection (the common SLL type), and the ventricular outflow tract to the aorta was narrow owing to restriction at the level of the interventricular communication (Fig 4). In the remaining patient, the right ventricle was rightwards and adjacent to the right atrium, and the ventriculoarterial connection was transitional between the discordant and entire double outlet left ventricle. The interventricular communication did not appear to be an ultimate restrictive factor for the flow to the aortic channel.

Pulmonary stenosis was seen in 17 (40%), of whom 15 had discordant ventriculoarterial connections; 11 with the right ventricle leftwards and 4 with the right ventricle rightwards (Fig 4). The pulmonary valve orifice was squeezed between the outlet septum and the atrioventricular valves. In the other 2 with the right ventricle rightwards and concordant ventriculoarterial connection, the interventricular communication was restrictive to the pulmonary pathway. Pulmonary atresia was present in 2 patients with the right ventricle leftwards, and the aorta originated from the morphologic right ventricle.

The aorta was arising from the morphologic right ventricle in 28 of 29 patients with the right ventricle leftwards and in 6 of 14 patients with the right ventricle rightwards. Of these, 19 (56%) underwent surgical maneuvers, by either myectomy at the level of the interventricular communication or additional aortopulmonary

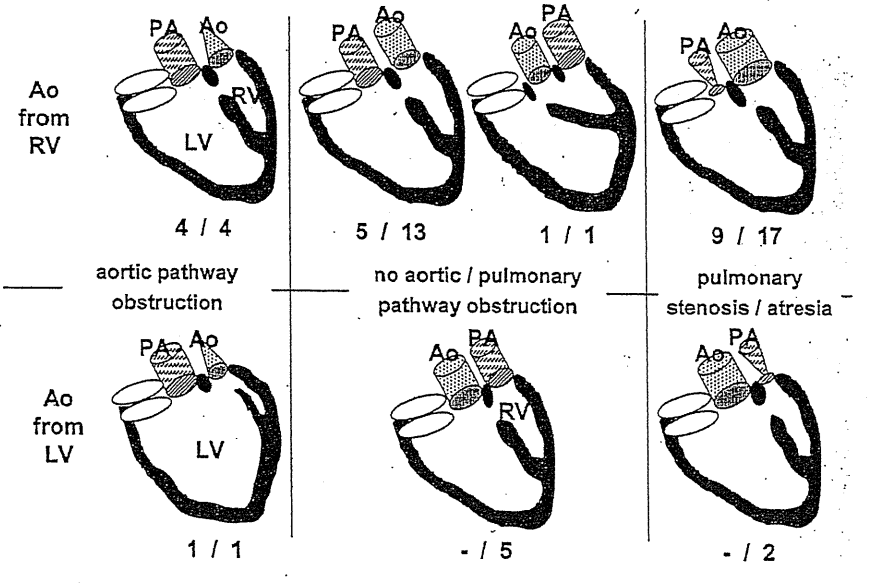

Fig 5. Diagrams of ventricular outflow tracts in clinical series in relation to outflow obstructions and surgical procedures used to avoid subaortic stenosis (by either the Damus-Kaye-Stansel anastomosis or enlargement of the interventricular communication). A set of the numbers indicates the number of the surgical procedures used for this purpose from the total number of each pattern of ventriculoarterial connection. Aortic pathway obstruction includes coarctation of the aorta, interruption of the aortic arch, or subaortic stenosis. (Ao = aorta; LV = morphologic left ventricle; PA = pulmonary arterial trunk; RV = morphologic right ventricle.)

anastomosis (the Damus-Kaye-Stansel anastomosis), to treat existing or potential subaortic stenosis (Fig 5). These included the 4 patients with obstruction of the aortic arch, 6 of 14 with no aortic coarctation or pulmonary stenosis (including 1 with double outlet right ventricle), 8 of 15 with pulmonary stenosis, and 1 of 2 with pulmonary atresia.

In the exceptional patient with the right ventricle leftwards, the ascending aorta was oriented left anteriorly to the pulmonary trunk. We initially presumed the ventriculoarterial connection was a double outlet right ventricle because of the presence of hypertrophied muscular trabeculations, but it turned out to be a double outlet left ventricle. This patient underwent banding of the pulmonary trunk as a first palliation, and we very cautiously monitored this patient until the next stage of surgical procedure; we anticipated progression of subaortic stenosis to a greater or lesser degree. Nonetheless, on ventriculography before the Fontan type procedure, we confirmed the presence of a rudimentary ventricle of the morphologic right type located leftwards, but it was not related to either of the great arteries. No subaortic narrowing has been noted for 9 years after the Fontan completion.

Only 1 of 8 patients with the right ventricle rightwards and the aorta arising mainly from the dominant left ventricle underwent surgical treatment for moderate subaortic stenosis. This patient's aorta was anterior to the pulmonary truck, and coarctation of the aorta was repaired during the neonatal period and the pulmonary trunk was banded. We regarded this patient also as a high-risk case for progressive subaortic stenosis; but contrary to our expectation, the subaortic region remained unobstructed. We subsequently inspected the subaortic channel through the aortic valve and through the atrial incision at the time of total cavopulmonary connection and noted a mild degree of overriding of the aorta (by 25%) to the small morphologic right ventricle. Because of the malalignment between the muscular ventricular septum and the outlet septum, the pathway to the aorta appeared sufficiently wide, and we did not use surgical maneuvers such as the Damus-Kaye-Stansel anastomosis or enlargement of the interventricular communication.

Nine years later, nonetheless, the pressure gradient between the dominant left ventricle and the ascending aorta was 37 mm Hg by catheter measurement. Although the degree of obstruction was moderate, there was a progressive decrease in ventricular contraction. The patient consequently underwent reoperation with excision of the outlet septum and removal of musculature from the crest of the ventricular septum. The pressure gradient dropped to 4 mm Hg during the procedure.

Comment

Stereotypes of double inlet left ventricle have been documented mainly by location of the hypoplastic and incomplete morphologic right ventricle (either rightwards or leftwards) in relation to the dominant morphologic left ventricle, as well as concordant or discordant ventriculoarterial connections [7]; namely, two multiplied by two equals four essential stereotypes. The combination of the right ventricle leftwards and concordant ventriculoarterial connections is known to be exceedingly rare [7] and was seen in 2 of the 97 examples of this study. The commonest stereotype is clinically known as the SLL type, which is a small and incomplete morphologic right ventricle being left-anteriorly located to the dominant morphologic left ventricle, with discordant ventriculoarterial connections in which the ascending aorta arises left anteriorly to the pulmonary trunk. It is well recognized that the interventricular communication frequently causes subaortic stenosis in this setting [8–10]. Historically, it is known that Holmes described in 1824 the concordant ventriculoarterial connection with double inlet atrioventricular connection to the left ventricle and the right ventricle rightwards (a small and incomplete morphologic right ventricle located right anteriorly to the dominant morphologic left ventricle) [4].

This "quartet" classification of morphologic spectrum is pertinent because tricuspid atresia is considered under a similar concept [11]. When we find an example of tricuspid atresia with double outlet right ventricle [12, 13], however, we question whether the quadradivision is adequate. As we have documented, unusual ventriculoarterial connections can have clinical relevance. In the patient who initially had coarctation of the aorta and eventually underwent relief of subaortic obstruction after the Fontan completion, perhaps, intervention to the ventricular outflow tract could have been applied earlier and prophylactically. The Damus-Kaye-Stansel anastomosis in this setting [14–16] could be over-indicated even in those who do not have eventually the potential for developing subaortic stenosis. Nonetheless, this remains debatable: The additional maneuver should better be avoided, if not really needed, because of another possible compromising factor, which is regurgitation across the semilunar valve additionally placed for the systemic circulation [17].

On the other hand, when the aorta and the pulmonary trunk both arise from the rudimentary and morphologic right ventricle that lacks an inlet component, the addition of an aortopulmonary anastomosis is unsuitable for relieving subaortic obstruction. Only enlargement of the interventricular communication can resolve the obstruction. Previously accumulated knowledge is of great help to avoid injury to the conduction bundle when the ventricular septum is incised [18], irrespective of ventriculoarterial connections.

These special considerations would not have been required in most hearts with double inlet left ventricle because the ventriculoarterial connections were of typical patterns in four-fifths of our series. Still, we should not ignore the remaining patterns, albeit uncommon, seen in a fifth of examples. Orientation of the great arteries was not predictive of the precise types of ventriculoarterial connections. An atypical ventriculoarterial connection can be present with usual orientation of the

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great arteries, whereas a common type of ventriculoarterial connection (concordant or discordant) may be the case with the aorta and the pulmonary trunk unusually located. The percentage of less typical variants appeared slightly higher than previously documented in the established textbook of cardiac surgery [6]. This probably reflects the background nature of the present materials, which is based on both clinical patients and autopsied specimens.

We also observed that there were transitional spectrums between concordant or discordant connections and double outlet right or left ventricle. Albeit a quadrapolar scheme is theoretically more precise than concordant-discordant resolution in the ventriculoarterial connection, overriding of one of the great arteries needs recognition. To note whether overriding is present, malalignment between the outlet septum and the muscular ventricular septum, as well as orientation of the aorta relative to the pulmonary trunk, must be described. These perceptive points are also of practical use in patients with pulmonary atresia. In this particular setting, the aorta frequently originated from the morphologic right ventricle (7 of 8 cases). The size and shape of the outlet septum and the degree of alignment of the structure to the rest of the ventricular septum vary. Whether the aortic pathway is potentially obstructive depends on the size of the interventricular communication. The presence of pulmonary atresia does not necessarily imply an unobstructed subaortic channel.

An obvious limitation of this study is the lack of physiologic consideration. It has been well documented that the size of the interventricular communication changes depending on the volume load conditions to the ventricles [9, 10, 16, 19]. Even in a typical double inlet left ventricle with the right ventricle leftwards and discordant ventriculoarterial connections, subaortic stenosis might not progress if the communication was truly large in diameter [6]; whereas, for example, 50% overriding of the aorta to the dominant left ventricle could have obstruction across the systemic ventricular outflow tract if the aortic orifice was notably small. In this respect, further quantitative analyses are needed. We nevertheless focused in the present study on morphologic and qualitative aspects to highlight atypical variants of ventriculoarterial connections that can exist in double inlet left ventricle and require careful assessment before deciding on optimal surgical strategy.

Besides the typical forms of double inlet left ventricle with discordant or concordant ventriculoarterial connection, less frequent but important patterns were present that had surgical relevance for ventricular outflow obstruction. The four headings of concordant, discordant, double outlet right, double outlet left, and the transitional spectrums between these require recognition. When the aorta arises from the morphologic right ventricle, the subaortic channel requires particular attention for potential obstruction.

Hideki Uemura was working at the National Cardiovascular Center of Japan between May 1988 and March 2004 when part of this study was done.

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INVITED COMMENTARY

Uemura and associates [1] describe the anatomic patterns encountered in a cohort of almost 100 patients with double inlet left ventricle, with just over half of their cohort studied subsequent to death of the patient and autopsy, but with the remainder assessed in the clinical setting. As they indicate, it is usual for patients with double inlet left ventricle to be stratified according to the location of the incomplete and rudimentary right ventricle relative to the dominant left ventricle, with two-thirds of their cohort having the most common pattern in which the incomplete right ventricle is left-sided. This situation is usually taken to be the consequence of left-handed ventricular looping during development, although perhaps sensibly, the authors do not venture into the potential minefield of embryological speculation.

Only 2 of their patients with leftward right ventricles had concordant ventriculoarterial connections, a combination which the authors stress as being very rare. Most of their patients, therefore, could be placed into the three anatomic stereotypes of leftward right ventricle with discordant ventriculoarterial connections, the commonest pattern, or rightward right ventricle with either discordant or concordant ventriculoarterial connections. These latter two stereotypes were present in almost equal numbers in their series.

The pattern with rightward right ventricle and concordant ventriculoarterial connections has historical connotation, being first described in 1842 by Andrew Holmes [2], and now universally recognized as the Holmes heart. As much as one-quarter of the cohort, nonetheless, could not be fitted into these stereotypical patterns. This was because of unexpected ventriculoarterial connections, such as double outlet from the dominant left or the incomplete right ventricle, because of the presence of pulmonary atresia, or else because the relationship of the arterial trunks was not anticipated for the given ventriculoarterial connection. Their study confirms that patients with so-called complex lesions always require full sequential segmental analysis, with attention always paid separately to the connections present between the cavities of the adjacent cardiac segments and the interrelationships of their component parts.

All of their patients bar one had usual atrial arrangement, and presumably a double inlet through 2 separate atrioventricular valves. This suggests a degree of selection in their series, because in the analysis made by Franklin and colleagues [3] of patients presenting clinically in the first year of life, only 113 of 136 patients with double inlet left ventricle had a usual atrial arrangement, with 19 having isomeric atrial appendages, or so-called visceral heterotaxy. Of this latter series, 42 of 136 had a common atrioventricular valve, another feature of major clinical significance.

It is the 2 patients described by Uemura and colleagues [1] with leftward right ventricles and concordant ventriculoarterial connections that arouse my own particular interest. They suggest that these patients could be described as having "anatomically corrected malposition." In fact, when there are spiralling arterial trunks, with the pulmonary trunk arising to the left of the aorta, if a descriptive term is to be used, the arrangement would be called "isolated ventricular inversion." This is because when there is usual atrial arrangement and usual spiralling of concordantly connected arterial trunks, it is the leftward location of the right ventricle that is isolated in terms of intersegmental relationships.

When the arterial trunks are concordantly connected in the setting of double inlet left ventricle and leftward incomplete right ventricle, albeit a very rare event, it is more usual for the trunks to exit from the heart in parallel fashion, with the aorta to the left. It is this latter combination that could then be described as anatomically corrected malposition. We recently described several autopsied specimens with the latter arrangement [4]. The cases described by Uemura and colleagues [1], with spiralling arterial trunks, leftward incomplete right ventricle, and concordant ventriculoarterial connections constitute an exceedingly rare combination that, to the best of my knowledge, has not previously been described.

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Which Factors Predict the Recovery of Natural Heart Function After Insertion of a Left Ventricular Assist System?

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Background: Recent reports have demonstrated that use of a left ventricular assist system (LVAS) can initiate recovery of cardiac function, and subsequent weaning from the LVAS has attracted considerable interest. In this study we investigated reliable predictors of LVAS weaning.

Methods: Eighty-two patients underwent LVAS implantation between April 1994 and July 2006 at our institution. Cardiac function was restored in 8 patients, who were weaned from LVAS after a mean of 5 months (Group R). Thirty-three patients remained on LVAS support for >1 year (Group N) because natural heart function did not show adequate improvement. We retrospectively evaluated the differences between these two groups. Group R was younger, and had a shorter duration of heart failure than Group N (23.4 vs 36.7 years and 13.3 vs 56.1 months, $p < 0.01$, respectively). Pathologic findings showed that the interstitial fibrosis score was lower in Group R ($p < 0.01$). Three months after LVAS insertion, B-type natriuretic peptide (BNP) and fractional shortening (FS) were more favorable (66.6 ± 46 vs 264.5 ± 170 pg/ml, $p < 0.01$, and 23 ± 17.1 vs 12 ± 9.1%, $p < 0.05$, respectively) in Group R. Furthermore, Group R received a higher dose of β-blocker (15.4 ± 8.4 vs 5.8 ± 3.9 mg, $p < 0.05$).

Conclusions: Younger age, shorter history of heart failure, and less interstitial fibrosis were effective predictors of weaning from LVAS. Restoration of natural heart function was more rapid and more persistent in candidates for LVAS explantation, and presence of β-blocker played a prominent role in improving cardiac function after LVAS implantation. J Heart Lung Transplant 2008;27:869-74. Copyright © 2008 by the International Society for Heart and Lung Transplantation.

The left ventricular assist system (LVAS) is a powerful tool for saving patients with end-stage heart failure. The primary objective of this device is to provide sufficient circulation, to help patients recover from secondary organ dysfunction, and to stabilize them until their own heart function recovers or suitable donor organs are found. However, relatively few patients receive the benefit of heart transplantation, especially in Japan, due to a shortage of donor organs. In a previous study, we have described the possibility of natural heart recovery after profound heart failure using long-term LVAS support.[1] Several recent reports have demonstrated the restoration of native cardiac function during LVAS support, and weaning from LVAS is recognized as a desirable option. Several factors are associated with improvement of natural heart function after LVAS implantation. Levin et al reported reverse remodeling with a decreased LV mass in LVAS-supported patients.[2] Reduced cellular edema,[3] improved myocardial metabolism,[4] reversal of neurohumoral stimulation[5] and decreased apoptosis[6] have also been suggested. Assessment of myocardial recovery during LVAS support is also an area of interest.[7] However, it remains unclear which patients are appropriate candidates for LVAS explantation. In this study we investigated the factors that could predict weaning from LVAS.

METHODS

Patient Population

Between April 1994 and July 2006, 82 patients except post-cardiotomy cases underwent LVAS implantation for end-stage heart failure at our institution. All patients had New York Heart Association Class IV status and were supported by intravenous inotropic agents and/or percutaneous mechanical support. Among these patients, natural heart function was restored and general condition was sufficiently stable in 8 patients (ages 17

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to 38 years, 7 males and 1 female; 7 with dilated cardiomyopathy [DCM], 1 with myocarditis) and they were weaned from LVAS after 89 to 310 days (recovery group: Group R). Thirty-three patients were supported by LVAS for >1 year. They remained generally stable, but they could not be weaned from LVAS because of poor native heart function (non-recovery group: Group N). This group comprised 22 males and 11 females, ages 16 to 55 years, and whose etiologies were as follows: 27 had DCM; 3 were in the dilated phase of hypertrophic cardiomyopathy (dHCM); and 3 had secondary cardiomyopathy (sarcoidosis, myopathy and drugs). Of these, 15 patients underwent heart transplantation, 13 died (6 cerebral hemorrhages, 1 cerebral infarction, 6 infections), and 5 remain on the waiting list. Another 3 patients were weaned from LVAS due to cerebral events despite insufficient natural heart recovery. LVAS support was discontinued within 1 year in the other 35 patients because of transplantation or death.

In Group R, 3 patients were given a Toyobo LA LVAS, 4 a Toyobo LV LVAS and 1 a Novacor device. In Group N, 30 patients were given a Toyobo LV LVAS and 3 a HeartMate VE device. We retrospectively evaluated the differences between Group R and Group N. To assess natural heart function, we followed-up echocardiographic parameters and the brain natriuretic peptide (BNP) levels at 1 and 3 months after LVAS implantation. Medical therapy regimens were also evaluated. The investigations complied with the principles outlined in the Declaration of Helsinki. The study was approved by the institutional review board of the National Cardiovascular Center, and all patients provided written informed consent.

Management After LVAS Implantation

After general stabilization, we re-administered a β-blocker (carvedilol), an angiotensin-converting enzyme inhibitor (ACE-I, enarapril) and an aldosterone antagonist (spironolactone).

The maximum titrated doses were 20, 5 and 25 mg, respectively. The criteria by which we introduced or increased these drugs were as follows: systolic blood pressure >80 mm Hg; heart rate >60 beats/min; and no sign of deterioration of heart failure. Adequate rehabilitation was also combined with medical treatments. Nutritional states were assessed and the patients received nutritional intervention if necessary. The pump rate was gradually reduced to 60/min when cardiac function showed no deterioration.

Weaning Protocol

Device explantation was considered if the patients met the following criteria: left ventricular diameter in diastole (LVDd) <55 mm; fractional shortening (FS) >20%; and BNP < 100 pg/ml under minimal LVAS support (60 pumps/min). Candidates for LVAS explantation then underwent dobutamine stress testing. Dobutamine was titrated from 5 to 40 μg/kg/min, and hemodynamic and echocardiographic data were evaluated at each dose level. The test outcome was classified as favorable if the patients showed an increase in cardiac output and FS with an increase in dobutamine, without an increase in pulmonary capillary wedge pressure (PCWP), LVDd and symptoms of heart failure. Those who responded appropriately to dobutamine stress testing were considered candidates for LVAS explantation.

Statistical Analysis

We used Student's unpaired *t*-test to compare continuous variables (all data expressed as mean ± SD) and the chi-square test to compare categoric variables. In time-course analysis (Figure 1), data were analyzed by 2-way analysis of variance (ANOVA) followed by Tukey's post hoc test. $p < 0.05$ was considered statistically significant. All analyses were performed using SPSS software (version 14-J).

RESULTS

Before LVAS Implantation

Table 1 summarizes the demographics and baseline characteristics of Groups R and N. Group R was significantly younger and had a shorter duration of heart failure than Group N ($p < 0.01$, respectively). Group R had less myocardial fibrosis than Group N ($p < 0.01$). Myocardial hypertrophy tended to be milder in Group R, but the difference did not reach statistical significance. The ratio (%) of patients with dilated cardiomyopathy was similar in both groups. Hemodynamic parameters, echocardiographic parameters, dose of intravenous inotropic agents, ratio (%) of patients supported by percutaneous mechanical assist devices, BNP levels, and degree of other organ dysfunction or anemia did not significantly differ between the two groups. The regimens of medical treatment did not significantly differ between the two groups (Table 2), but the percentage of patients who were given an ACE-I, a β-blocker, a spironolactone or an amiodarone tended to be higher in Group N.

One Month After LVAS Implantation

Echocardiographic parameters (Dd and FS) and BNP levels were more favorable in Group R, but the differences were not statistically significant (Table 3). The ratio (%) of patients who tolerated treatment with a β-blocker was significantly higher in Group R ($p < 0.05$) (Table 4).

Three Months After LVAS Implantation

FS was significantly higher, and BNP levels was significantly lower ($p < 0.05$ and $p < 0.01$, respectively) in Group R than in Group N (Table 5). Furthermore, the

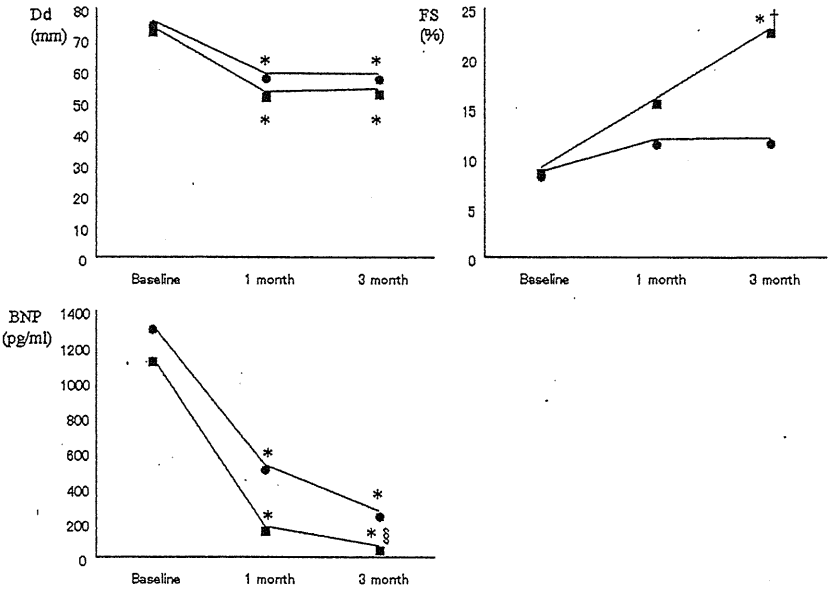

Figure 1. Changes in Dd, FS and BNP after LVAS implantation. Filled squares: Group R; filled circles: Group N. $^{*}p < 0.05$ vs baseline, $^{\dagger}p < 0.05$ vs Group N and $^{\S}p < 0.01$ vs Group N. LVDd, left ventricular end-diastolic dimension; FS, fractional shortening; BNP, brain natriuretic peptide.

increasing rate of FS and the decreasing rate of BNP (3 months after vs before LVAS implantation) were significantly higher in Group R ($p < 0.05$, respectively, data not shown). The dose of β-blocker was higher in Group R ($p < 0.05$) (Table 6). More patients tolerated treatment with an ACE-I or a β-blocker, and Dd tended to be smaller in Group R, but statistical significance was not demonstrated.

Time Course After LVAS Implantation

Figure 1 shows changes in Dd, FS and BNP after LVAS implantation. Improvement of Dd was almost complete

Table 1. Demographics and Baseline Characteristics of Study Population

	Group R ($n = 8$)	Group N ($n = 33$)	p-value
Age (years)	23.4 ± 7.1	36.7 ± 12.4	<0.01[a]
Gender (% female)	12.5	35.3	0.21
Etiology (% dilated cardiomyopathy)	87.5	79.4	0.6
Duration of heart failure (month)	13.3 ± 22	56.1 ± 52	<0.01[a]
Myocardial fibrosis (score)	1.4 ± 0.5	2.5 ± 0.6	<0.01[a]
Myocardial hypertrophy (score)	1.7 ± 0.5	2.2 ± 0.8	0.1
Dose of inotropic agents (DOA + DOB)	9.7 ± 5.6	10.2 ± 4.8	0.83
Use of mechanical support (% IABP and/or PCPS)	62.5	67.6	0.78
Systolic blood pressure (mm Hg)	93 ± 9.0	86 ± 12	0.16
Heart rate (bpm)	116 ± 13	103 ± 25	0.19
Cardiac output (liters/min)	3.21 ± 1.0	3.36 ± 1.0	0.77
Pulmonary capillary wedge pressure (mm Hg)	27.2 ± 4.3	27.2 ± 8.5	0.1
Right atrial pressure (mm Hg)	14.2 ± 5.8	10.2 ± 6.1	0.17
Left ventricular diastolic dimension (mm)	74.1 ± 8.9	75.9 ± 11	0.66
Fractional shortening (%)	9.0 ± 3.7	8.6 ± 4.6	0.84
Wall thickness (mm)	7.6 ± 0.4	7.4 ± 1.4	0.7
B-type natriuretic peptide (pg/ml)	1,140 ± 660	1,282 ± 1,074	0.76
Total bilirubin (mg/dl)	2.6 ± 1.0	1.8 ± 1.0	0.06
Creatine (mg/dl)	1.1 ± 0.5	1.4 ± 1.1	0.52
Hemoglobin (g/dl)	11.4 ± 2.5	10.5 ± 1.8	0.31

Myocardial fibrosis or hypertrophy was classified as mild, moderate or severe and scored as follows: 1 = mild; 2 = moderate; 3 = severe. Dose of inotropic agents is shown as the sum of dopamine (DOA) + dobutamine (DOB). Wall thickness is shown as the mean of the septum and posterior wall. IABP, intra-aortic balloon pump; PCPS, percutaneous cardiopulmonary support.

[a]Statistically significant.

Table 2. Medical Regimens Before LVAS Implantation

	Group R	Group N	*p*-value
ACE-I (%)	37.5	55.9	0.35
β-blocker (%)	12.5	47.1	0.07
Furosemide (%)	100	82.4	0.2
Spironolactone (%)	25	55.9	0.12
hANP (%)	37.5	23.5	0.42
Amiodarone (%)	12.5	50	0.05
Digitalis (%)	37.5	29.4	0.66

Ratio (%) represents drug induction rate. LVAS, left ventricular assist system; ACE-I, angiotensin-converting enzyme inhibitor.

within 1 month in both groups. Augmentation of FS continued during the follow-up period in Group R, but was complete at about 1 month in Group N. BNP levels decreased during the first month and continued to decrease thereafter in both groups.

Prognosis of Patients After LVAS Explantation

Table 7 shows prognosis of patients after LVAS explantation. Three of 8 patients have continued to maintain normal ventricular function during follow-up periods ranging from 8 months to 8 years. Four patients developed recurrent but mild heart failure, and were treated in the outpatient clinic for up to 10.5 years. All are being given an ACE-I (enarapril, mean dose 3.75 mg) and a β-blocker (carvedilol, mean dose 16 mg). The other patient did well up to 8 to 9 years after LVAS removal, but then had episodes of heart failure that required re-LVAS implantation 12 years after explantation. He is now on the waiting list.

DISCUSSION

This study has demonstrated that: (1) young patients with a short history of heart failure and less myocardial fibrosis are candidates for LVAS removal; (2) patients who can be weaned from LVAS show rapid and persistent improvement of natural heart function; and (3) a β-blocker is a potent agent that can induce LVAS removal.

Several mechanisms about restoration of the natural heart by LVAS have been reported. Wohlschlaeger et al showed that ventricular pressure and volume unloading by LVAS reduces harmful neurohumoral and cytokine stimulation (systemic and local), and decreases myocardial apoptosis.[8] Heerdt et al suggested that LVAS support increases the gene and protein levels of SERCA 2a, normalizes Ca^{2+} handling[9] and improves myocardial contraction. Brodde et al demonstrated an up-regulation of a β-receptor after LVAS support.[10] The regression of myocyte hypertrophy and interstitial fibrosis has been also suggested.[11,12] These effects, which occur as a result of maximal ventricular unloading, lead to functional recovery of the native heart.

Basal cardiac states, however, might influence the process of functional improvement. Histologic analysis has demonstrated that less myocardial fibrosis is one of the predictors of LVAS weaning.[13] This finding was also demonstrated in our study. Furthermore, in the present study, myocardial hypertrophy tends to be less common in patients who could be weaned from the device, but a significant difference was not detected. Our study found that younger patients with a shorter duration of heart failure before LVAS implantation were suitable candidates for LVAS explantation. These features indicate less pre-operative myocardial degeneration. The timing of LVAS implantation is very important. LVAS implantation in necessary before myocardial damage becomes irreversible for restoration of natural heart after LVAS implantation. Cardiac function and dysfunctional severity of other organs before LVAS implantation were not statistically different between Groups R and N.

The process of natural heart improvement might reach completion within 4 to 5 months after device implantation.[14] Continued ventricular unloading be-

Table 3. Echocardiographic Parameters and BNP Levels 1 Month After LVAS Implantation

	Group R	Group N	*p*-value
Left ventricular diastolic diameter (mm)	53.7 ± 12.4	59.5 ± 17.6	0.42
Fractional shortening (%)	16.1 ± 12.7	11.9 ± 7.7	0.43
BNP (pg/ml)	176.8 ± 151.6	526.2 ± 483.8	0.09

BNP, B-type natriuretic peptide; LVAS, left ventricular assist system.

Table 4. Medical Regimens at 1 Month After LVAS Implantation

	Group R	Group N	*p*-value
ACE-I (%)	71.4	41.2	0.14
β-blocker (%)	71.4	26.5	<0.05[a]
Furosemide (%)	85.7	88.2	0.85
Spironolactone (%)	57.1	70.6	0.49
Amiodarone (%)	0	20.6	0.19
Digitalis (%)	57.1	26.5	0.11

Ratio (%) represents drug induction rate. LVAS, left ventricular assist system.
[a]Statistically significant.

Table 5. Echocardiographic Parameters and BNP Levels 3 Months After LVAS Implantation

	Group R	Group N	*p*-value
Left ventricular diastolic diameter (mm)	54.7 ± 11.7	58.9 ± 15.4	0.49
Fractional shortening (%)	23.0 ± 17.1	12.0 ± 9.0	<0.05[a]
BNP (pg/ml)	66.6 ± 46.1	264.6 ± 170.1	<0.01[a]

BNP, B-type natriuretic peptide; LVAS, left ventricular assist system.
[a]Statistically significant.

Table 6. Medical Regimens at 3 Months After LVAS Implantation

	Group R	Group N	*p*-value
ACE-I (%)	85.7	55.9	0.14
β-blocker (%)	85.7	55.9	0.14
β-blocker (mg)	15.4 ± 8.4	5.8 ± 3.9	<0.05[a]
Furosemide (%)	57.1	85.3	0.09
Spironolactone (%)	57.1	70.6	0.49
Amiodarone (%)	57.1	32.4	0.22
Digitalis (%)	57.1	29.4	0.16

Ratio (%) represents drug induction rate. LVAS, left ventricular assist system; ACE-I, angiotensin converting enzyme inhibitor.
[a]Statistically significant.

yond this time frame may induce myocardial atrophy and fibrosis. Farrar et al reported that waiting 50 days would capture half of the patients who would ultimately recover ventricular function followed by successful device removal, and waiting up to 90 days could capture 80% of them.[5] We evaluated several parameters at 1 and 3 months after LVAS implantation. Natural heart function was restored more rapidly and the improvement persisted for longer in the weaned patients (Group R). They recovered completely, essentially within 3 months, and were weaned from LVAS after a mean of 5 months of support. BNP was the first representative indicator of native cardiac recovery, which was followed by echocardiographic improvement. None of the patients in whom restoration of the native heart was not indicated for these periods could be weaned from LVAS. This timing is compatible with the findings of Farrar et al.

Recently, the β-blocker has been recognized as being highly beneficial for patients with chronic heart failure, and is becoming the first-line drug treatment for heart failure.[15-17] However, the effect of a β-blocker in patients with LVAS is unclear. We found here that the ratio (%) of patients who tolerated treatment with a β-blocker at 1 month after LVAS insertion and the dose of a β-blocker at 3 months after device implantation were significantly higher in weaned than in non-weaned patients. This result indicates that a β-blocker is useful in patients with LVAS. Several mechanisms underlying the favorable effects of β-receptor blockage have been suggested. A β-blocker restores the function of the calcium-release channel and improves cardiac muscle performance.[18] It also improves myocardial energetics, attenuates myocardial apoptosis, and abrogates induction of the fetal gene program.[19] These effects ultimately help to prevent and reverse ventricular remodeling. Also, these mechanisms might strengthen restoration of the natural heart induced by LVAS. Our findings directly show the importance of β-blocker treatment in patients with first-time LVAS. The percentage of patients who tolerated treatment with an ACE-I after LVAS implantation was also higher in the weaned group, but the values did not reach statistical significance. Conversely, more patients were given a β-blocker, ACE-I, spironolactone and amiodarone before LVAS implantation in the non-weaned group. This may be dependent on the longer duration of heart failure in those patients.

Study Limitations

The present study has several limitations. First, the population size in this investigation was relatively small because the percentage of patients able to be weaned from LVAS is small. Second, the etiologies of patients are various due to the same reason (we could not focus specifically on DCM patients). Third, we demonstrated the effect of a β-blocker. However, we could not standardize the medical regimens after LVAS implantation. Further examinations on larger numbers of patients with uniform etiology and medical treatments are necessary.

In conclusion, weaning from LVAS might be feasible in selected patients. Adjunctive treatments as well as adequate unloading are important in those who

Table 7. Prognosis After Explanation of the Left Ventricular Assist System

Patient no.	Age (years)	Gender	Left ventricular diastolic dimension (mm)	Fractional shortening (%)	B-type natriuretic peptide (pg/ml)	New York Heart Association class	Current status	Duration after explantation
1	29	M	69	5	124	I	Re-LVAS implantation, in hospital, on waiting list	12 years
2	31	M	66	17	103	II	Well, at home	10 years 5 months
3	33	M	50	28	12	I	Well, at home	8 years
4	44	F	53	36	21	I	Well, at home	5 years 7 months
5	25	M	69	10	548	I	Well, at home	5 years 5 months
6	30	M	72	8	275	II	Well, at home	4 years 1 month
7	19	M	91	12	848	II	Well, at home	3 years
8	26	M	51	31	26	I	Well, at home	8 months

have the capability of natural heart restoration. Further studies on LVAS weaning are desirable.

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Activation of cardiac progenitor cells through paracrine effects of mesenchymal stem cells

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ABSTRACT

Mesenchymal stem cells (MSC) transplantation has been proved to be promising strategy to treat the failing heart. The effect of MSC transplantation is thought to be mediated mainly in a paracrine manner. Recent reports have suggested that cardiac progenitor cells (CPC) reside in the heart. In this study, we investigated whether MSC had paracrine effects on CPC in vitro. CPC were isolated from the neonatal rat heart using an explant method. MSC were isolated from the adult rat bone marrow. MSC-derived conditioned medium promoted proliferation of CPC and inhibited apoptosis of CPC induced by hypoxia and serum starvation. Chemotaxis chamber assay demonstrated that MSC-derived conditioned medium enhanced migration of CPC. Furthermore, MSC-derived conditioned medium upregulated expression of cardiomyocyte-related genes in CPC such as β-myosin heavy chain (β-MHC) and atrial natriuretic peptide (ANP). In conclusion, MSC-derived conditioned medium had protective effects on CPC and enhanced their migration and differentiation.

Mesenchymal stem cells (MSC) transplantation has been proved to be promising strategy to treat ischemic heart disease [1–4]. We and others have demonstrated therapeutic potency of MSC transplantation for the treatment of cardiovascular disease [5]. The effect of MSC transplantation is thought to be mediated by the supply of cell protective, angiogenic and mitogenic factors, in addition to differentiation of transplanted MSC into specific cell types [6–8]. However, the underlying mechanisms of MSC therapy remain unclear.

Cardiomyocytes have been traditionally regarded as terminally differentiated cells that compensate for cardiac dysfunction through hypertrophy. However, recent reports suggested that multipotent cells reside in the adult heart and differentiate into smooth muscle cells, endothelial cells and cardiomyocytes [9–11]. Cardiac stem cells (CSC) transplantation has been shown to decrease the infarct size and improve cardiac performance in a rat model of myocardial infarction [9]. These findings suggest that CSC may play an important role in cardiac regeneration. However, some problems including isolation and expansion of CSC remain to be unresolved for clinical application of CSC transplantation. Thus, a novel strategy to activate endogenous CSC would be desirable for the treatment of heart failure. Recently, recombinant hepatocyte growth factor (rHGF) was reported to promote migration and survival of endogenous CSC [12].

We have shown that MSC secret a number of cytokines and growth factors including HGF, vascular endothelial growth factor (VEGF) and insulin-like growth-1 (IGF-1) [4–6]. Therefore, we hypothesized that transplanted MSC-derived cytokines might activate endogenous cardiac stem/progenitor cells, leading to improvement in cardiac function of the failing heart. Thus, the purpose of this study was to investigate whether transplanted MSC activate endogenous cardiac progenitor cells (CPC) by enhancement of proliferation, migration and differentiation of CPC in a paracine manner.

Materials and methods

Isolation and expansion of mesenchymal stem cells from rat bone marrow. All protocols were performed in accordance with the guidelines of the Animal Care Committee of the National Cardiovascular Center Research Institute, Japan. Isolation and expansion of MSC were performed according to previously described methods [2]. In brief, we used 6- to 8-week-old male Lewis rats (Japan SLC, Hamamatsu, Japan) and harvested their bone marrow by flushing the femoral and tibial cavities with phosphate-buffered saline

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