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Comparison of prognostic variables in children and adults with Fontan circulation

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ABSTRACT

Background: Non-cardiac complications, such as hepato-renal and metabolic problems, are emerging late after the Fontan operation due to its unique hemodynamics. Consequently, associations between clinical variables and postoperative outcome may change during the prolonged postoperative course.
Methods and results: To determine if child and adult Fontan patients differ in the impact of cardiac and non-cardiac variables on clinical outcome, we prospectively evaluated associations between hemodynamics, neurohumoral factors, exercise variables, hepato-renal function and metabolic variables and unscheduled hospitalization, including death in 167 consecutive child and 116 adult Fontan patients. When compared with child patients, the adult patients showed higher rates of medications, lower cardiac index, higher values of natriuretic peptides, greater renal dysfunction, more cholestatic livers, and more impaired responses to exercise ($p < 0.05$–0.0001). During the follow-up of 3.7 ± 2.1 years, 64 clinical events (37 in adults), including 13 deaths, occurred. A high CVP and low arterial oxygen satutration strongly predicted the child events ($p < 0.001$), whereas these prognostic parameters were marginal in the adults. Instead, renal dysfunction and metabolic abnormality predicted adult events ($p < 0.05$). Neurohumoral activation, low albumin, hyponatremia, and impaired exercise variables equally predicted clinical events in child and adult Fontan patients.
Conclusions: Distinctive differences in predictive value of clinical variables exist between child and adult Fontan patients. In addition to cardiac issues, we should consider non-cardiac determinents of clinical outcome to maximize our efforts to improve prognosis for adult Fontan survivors.

Owing to recent advances in surgical and perioperative management, most post-Fontan patients now reach adulthood [1]. Fontan patients encounter arrhythmias, heart failure, and other clinical events, including death, as they age because of multiple substrates for arrhythmias and the palliative nature of the hemodynamics [2,3]. Recent studies have also demonstrated glucose metabolic abnormalities along with of liver and kidney dysfunction [4–6]. Possibly these "non-cardiac" pathophysiologies adversely influence morbidity and mortality and to date many clinical variables have been evaluated as to how they might associate with morbidity and mortality in Fontan patients [7–12]. In addition to established clinical variables, "non-cardiac" pathophysiologies may be more significantly involved in deterioration in adult Fontans than in children. Furthermore, the established prognostic values of clinical variables, such as central venous pressure (CVP), may change over time in this situation. To confirm this hypothesis, we prospectively evaluated cardiac and non-cardiac clinical variables and compared their impacts on the morbidity and mortality in child and adult Fontan patients.

1. Methods

1.1. Subjects

Since May 1980, 369 patients have undergone cardiac catheterization in our institute to evaluate their postoperative hemodynamics at least 6 months after the Fontan repair. Of those, 340 underwent their initial Fontan operation in our institution and the other 29 elsewhere. Our Fontan follow-up policy has included routine cardiac catheterization every 5 years post-operation to evaluate hemodynamics and exercise performance for all patients [11]. Among those patients, from January 2006 to December 2012, we prospectively studied 283 clinically stable Fontan patients (age 6 to 55 years) and they consisted of those ≥6 years old who were able to perform cardiopulmonary exercise testing (CPX). Clinical stability implied freedom from intravenous medications with no major change of oral medications and a postoperative follow-up of at least 3 months. Two-hundred and seventy patients had had a cavopulmonary connection (TCPC) and 13 an atriopulmonary connection (APC). We divided our patients into two groups according to age <18 years old (children, mean = 10 ± 4 years, $n = 167$) and age ≥18 years (adults, mean = 24 ± 6 years, $n = 116$). Our patients included 22 (14 in children) with protein

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Table 1
Subject characteristics.

	Total	Adults	Children
n	283	116	167
Age (yr)	16 ± 8	24 ± 6	10 ± 4
Height (cm)	145 ± 21	161 ± 8	133 ± 19
Weight (kg)	40 ± 16	53 ± 11	31 ± 13
Body mass index (kg/m)	18 ± 4	20 ± 4	16 ± 3
Age at Fontan (yr)	5 ± 6	9 ± 8	3 ± 2
Follow-up (yr)	9 ± 8	15 ± 6	8 ± 3
SV type (LV/non-LV)	113/171	56/60	57/111
Diagnosis			
Heterotaxy	79 (28%)	27 (23%)	52 (32%)
UVH	78	32	46
TA	62	34	28
DORV	49	16	33
MA	23	12	11
CAVC	18	4	14
PA	23	11	12
HLHS	10	0	10
Others	20	7	13
Type of repair			
APC	12	10	2
IAR	80	60	20
ECR	191	46	145
Previous or additional procedures at Fontan			
APS	160	69	91
PAB	78	20	58
Glenn	136	29	107
Fenestration	37	14	23
Medications (%)			
Diuretics	46	51	43
Anti-coagulant	77	71	81
ACEI/ARB	30	36	25
Beta blocker	20	29	13
Anti-arrhythmia	12	16	7

ACEI = angiotensin converting enzyme inhibitor, APC = atriopulmonary connection, APS = aortopulmonary shunt, ARB = angiotensin receptor blocker, AVVP/R = atrioventricular valve plasty/replacement, CAVC = common atrioventricular canal, DORV = double outlet right ventricle; ECR = extracardiac rerouting, HLHS = hypolastic left heart syndrome, IAR = intraatrial rerouting, LV = left ventricle, MA = mitral valve atresia, PA = pulmonary valve atresia, PAB = pulmonary artery banding, SV = systemic ventricle, TA = tricuspid.

losing enteropathy. Medications and history of surgical procedures are described in Table 1. The study protocol was approved by the Ethics Committee of the National Cerebral and Cardiovascular Center.

2. Assessment of hemodynamics, systemic ventricular and atrioventricular valvular functions

Cardiac catheterization was performed in 165 child and 114 adult patients within 1 week of CPX. We measured pressures in the cardiac chambers and great vessels, estimated oxygen consumption from the age, sex, and heart rate, and measured cardiac index (l/min/m^2) using the Fick principle assuming equal right and left pulmonary arterial saturations in patients with either a Glenn or a TCPC because it is difficult to measure accurate flow distribution in the bilateral pulmonary arteries. Ventricular morphology was determined by echocardiography and/or cine-ventriculography and patients were divided into 3 groups [12], i.e., those with 1) a dominant left ventricle (LV) with or without a rudimentary right ventricle; 2) presence of both right and left ventricles; and 3) a dominant right ventricle with or without a rudimentary LV. In this study, each group consisted of 74, 35, and 58 children and 49, 10, and 57 adults, respectively. We used Simpson's rule to estimate morphological right and left ventricular volumes. End-diastolic ventricular volume was divided by body surface area to obtain end-diastolic volume index (EDVI) and systemic ventricular ejection fraction (EF) was calculated. The atrioventricular valve regurgitation was estimated by color flow mapping and graded as; none to mild, moderate, or severe.

2.1. Neurohumoral activities

After at least 15 min supine rest, the plasma levels of norepinephrine (NE), brain natriuretic peptides (BNP) and renin activity (PRA) were determined in 283, 283, and 260 Fontan patients, respectively [13–15].

2.2. Serum lipids, glucose, metabolic and biochemical variables

Biochemical variables included plasma albumin (g/dl), sodium (Na^+: mEq/l), creatinine, and blood urea nitrogen (mg/dl), liver enzymes, and total cholesterol (mg/dl). Glucose metabolic variables included fasting plasma levels of glucose (mg/dl) and insulin (μU/ml) and homeostasis model assessment (HOMA-IR) was used to assess insulin resistance [16].

2.3. Pulmonary function tests

We measured vital capacity (VC; l) and percent forced expiratory volume in 1 s (FEV1) in 110 child and 104 adult patients (Spirosift, SP-600, Fukuda Denshi, Tokyo) and VC was calculated as the percentage of the body height predicted normal value for Japanese children and adults [17].

2.4. Exercise protocol

Two hundred and sixty seven patients (152 children and 115 adults) underwent symptom-limited CPX on a treadmill [18] and peak oxygen uptake (VO_2) (ml/kg/min) was measured and calculated as the percentage of body weight predicted normal value for our institute. We used a twelve lead ECG to determine heart rate. Ventilation and gas exchange were measured using a breath-by-breath method. Minute ventilation versus carbon dioxide production slope ($VE–VCO_2$ slope) was determined from the start of ramp exercise to the respiratory compensatory point and expressed as the percentage of our normal values.

2.4.1. Prospective clinical events

Clinical events were defined as events requiring unscheduled hospitalizations (USHs) for management and included arrhythmias, heart failure, thromboembolisms, emergency catheter and/or surgical interventions and death from all causes. Protein losing enteropathy [6], including its relapse, and renal failure were also included. Heart failure was diagnosed if there was at least one of the following: orthopnea, nocturnal dyspnea, pulmonary edema, increasing peripheral edema, or radiological signs [19]. Hemoptysis and infectious endocarditis were also included as a cause of USH.

2.5. Statistical analysis

Differences in continuous clinical variables were evaluated using a Student *t* test between the child and adult Fontan groups. Comparisons of the prevalence of medications were evaluated with a chi-square test. We used Cox's proportional hazards model to predict the associations between the clinical variables and USHs, including all cause mortality. The variables that proved to be significant predictors of the outcome in the univariate analysis ($p < 0.05$) were included in the multivariate analysis to determine the independent predictors. In assessing the impact of systemic ventricular function, i.e., EF and EDVI, on the prognosis with Cox's model, the hazard ratios (HRs) were computed for intervals of 10 (%) for the EF and 20 (ml/m^2) for the EDVI to minimize the error of volume estimation with Simpson's rule. Sytemic ventricular type was divided into two categories, LV type and non-LV type. A free status from USHs was estimated using the Kaplan–Meier method and the differences in the event free status between the groups were assessed using log rank tests. A p value of <0.05 was considered statistically significant. Data are expressed as the mean ± SD. Analyses were performed with the software JMP 10 pro (SAS Institute, Cary, NC, USA).