Current Outcome and long-Term Complication of Fontan Operation

Hong Ryang Kil
Department of Ped. School of Medicine
Chungnam National University

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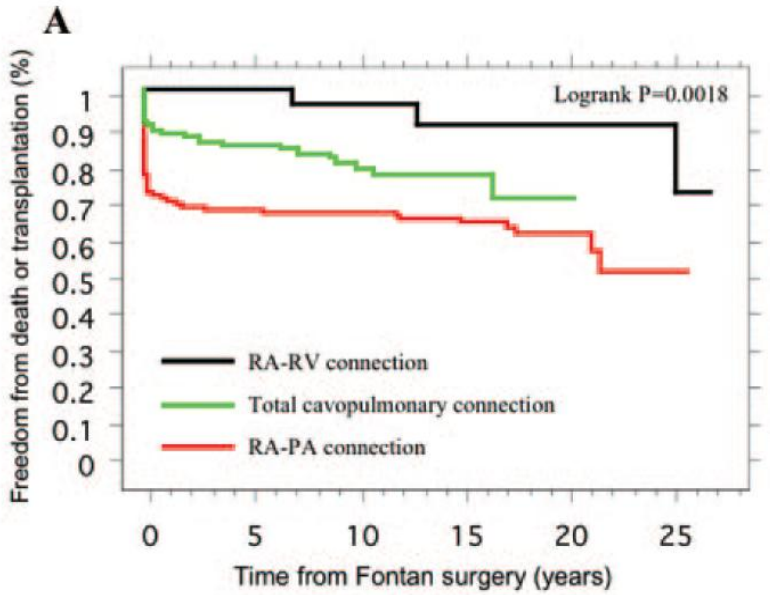
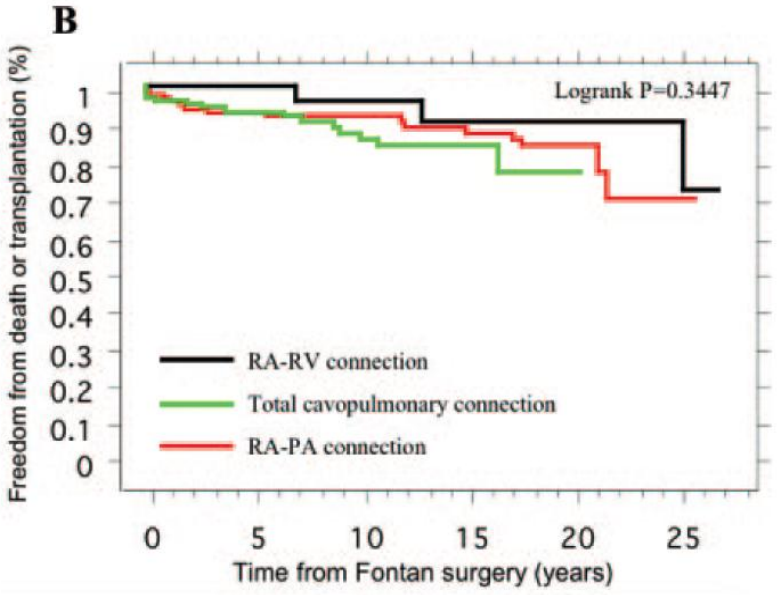
Long-Term Survival, Modes of Death, and Predictors of Mortality in Patients With Fontan Surgery



Number at risk						
RA-RV	25	25	20	14	10	6
TCPC	122	77	57	27	1	0
RA-PA	135	85	77	61	23	3
TOTAL	282	187	154	102	34	9

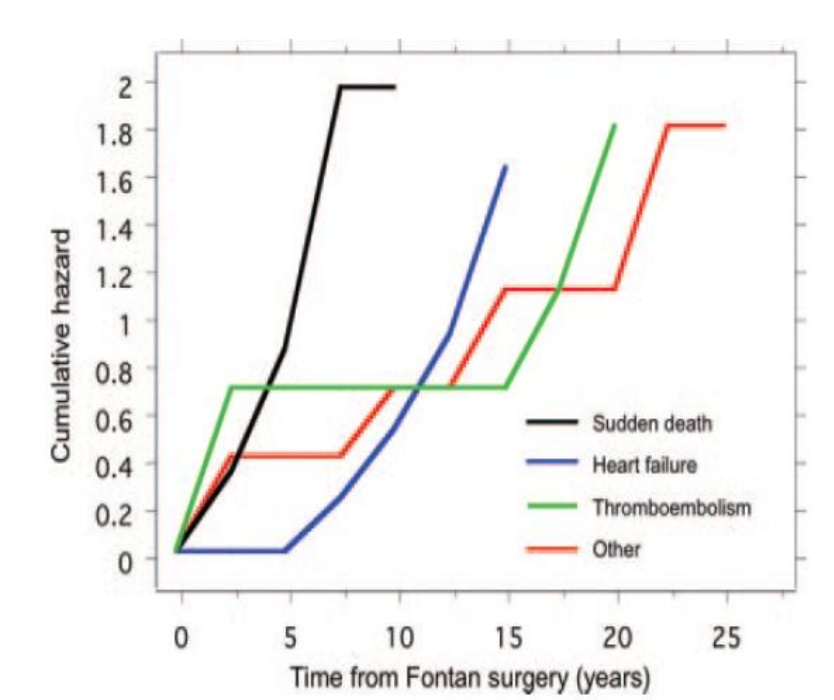


Number at risk						
RA-RV	25	25	20	14	10	6
TCPC	112	77	57	27	1	0
RA-PA	98	85	77	61	23	3
TOTAL	235	187	154	102	34	9

- 261 Patients born in 1985 or earlier with Fontan (Boston Children)
- First Fontan surgery at Median age of 7.9 year
- Mode of Fontan : AP 51% / RA-RV 9.6% / TCPC 38.7%
- PeriOP mortality account for 68.4% of all death

Paul Khairy. Circulation. 2008

Long-Term Survival, Modes of Death, and Predictors of Mortality in Patients With Fontan Surgery



- Thromboembolism(91% at 25y)
  - Median 24.9yr
  - 8.7yr after Fontan
- Heart failure(96% at 25y)
  - Median 22.9yr
  - 11.9yr after Fontan
- Sudden death(96.3% at 25yr)
  - Median 20.2yr
  - 2.9 after Fontan

Cumulative hazard by mode of death.

Death from 3 common cause

Paul Khairy. Circulation. 2008

Table 2. Predictors of All-Cause Mortality or Transplantation in Perioperative Survivors

Characteristic	Hazard Ratio	95% CI	*P*
Multivariate			
Protein-losing enteropathy	2.5	1.1–5.3	0.0217
Hypoplastic left heart syndrome	10.1	1.0–98.3	0.0472
RA pressure on follow-up, mm Hg	1.20	1.07–1.36	0.0023
Diuretic therapy	8.7	1.9–40.7	0.0058

CI indicates confidence interval; PVR, pulmonary vascular resistance.

Table 3. Predictors of Thromboembolic Death in Perioperative Survivors

Characteristic	Hazard Ratio	95% CI	*P*
Univariate			
Atrial fibrillation	5.4	1.0–29.4	0.0529
Lack of aspirin or warfarin therapy	5.7	1.0–32.3	0.0515
RA pressure on follow-up, mm Hg	1.26	1.03–1.53	0.0247
Thrombus within Fontan	4.9	2.1–11.6	0.0002
Multivariate			
Thrombus within Fontan	22.7	4.3–120.0	0.0002
Lack of aspirin or warfarin therapy	91.6	4.2–2004.8	0.0041

Table 4. Predictors of Heart Failure Death in Perioperative Survivors

Characteristic	Hazard Ratio	95% CI	*P*
Multivariate			
Protein-losing enteropathy	7.1	1.9–27.2	0.0043
Single right ventricle	10.5	1.1–100.4	0.0429
RA pressure on follow-up, mm Hg	1.30	1.05–1.62	0.0016

CI indicates confidence interval.

Paul Khairy. Circulation. 2008

Long-Term Survival, Modes of Death, and Predictors of Mortality in Patients With Fontan Surgery

- The leading cause of death - periOP, particularly in earlier era. The gradual attrition, thereafter, predominantly from 3 common causes
- Actual freedom from all-cause death or transplantation 70% at 25years
- The Incidence of Sudden death - 0.15%/yr, with most events of presumed arrhythmia origin

Paul Khairy. Circulation. 2008

Contemporary Outcomes After the Fontan Procedure

A Pediatric Heart Network Multicenter Study

- Recruited subject : 6-18 year
- Enrollment : 2003-2004

  546/644 eligible /total 1,078 from 7 center in US & Canada
- Similar Age, time since Fontan procedure, & functional health status score

Diagnosis	n	%
Tricuspid atresia	119	22
Hypoplastic left heart syndrome	112	21
Double inlet left ventricle	80	15
Heterotaxia	42	8
Double outlet right ventricle	41	8
Pulmonary atresia intact ventricular septum	33	6
Mitral atresia	31	6
Abnormal tricuspid valve	22	4
Atrioventricular canal defect	22	4
Other	38	7

Study Design and Sample

Cardiac Anatomic Dx

(Anderson, J Am Coll Cardiol 2008)

Fontan Cross-Sectional Study patient Characteristics by Age at Enrollment

Characteristic	n	Overall	<9 yrs	9 to <11 yrs	11 to <15 yrs	≥15 yrs	p Value
		Mean ± SD, Median, or %	Mean ± SD, Median, or %	Mean ± SD, Median, or %	Mean ± SD, Median, or %	Mean ± SD, Median, or %	
n		546	138 (25%)	120 (22%)	169 (31%)	119 (22%)	
Age at enrollment, yrs		11.9 ± 3.4	7.9 ± 0.7	10.0 ± 0.6	12.8 ± 1.2	17.0 ± 1.1	
Age at Fontan, yrs		3.4 ± 2.1	3.0 ± 1.3	3.0 ± 1.5	3.2 ± 1.9	4.6 ± 3.0	<0.001
Fontan type	513						<0.001
Atriopulmonary connection		13%	<1%	3%	15%	36%	
TCPC intracardiac lateral tunnel		59%	52%	62%	70%	50%	
TCPC extracardiac lateral tunnel		13%	26%	19%	4%	3%	
TCPC extracardiac conduit		13%	21%	15%	9%	6%	
Stage II surgery performed	546	75%	93%	88%	78%	35%	<0.001

(Anderson, J Am Coll Cardiol 2008)

Fontan Cross-Sectional Study Patient Characteristics by Age at Fontan Procedure

Characteristic	<2 yrs Mean ± SD, Median, or %	2 to <3 yrs Mean ± SD, Median, or %	3 to <4 yrs Mean ± SD, Median, or %	≥4 yrs Mean ± SD, Median, or %	p Value	Age-Adjusted p Value
n	113	191	104	138		
Age at enrollment, yrs	11.1	10.8	10.8	13.3	<0.001*	
Age at volume unloading surgery, yrs	0.9 ± 0.5	1.2 ± 0.8	1.7 ± 1.2	2.8 ± 2.4	<0.001	
Fontan type					<0.001	<0.001
Atriopulmonary connection	6%	15%	15%	15%		
TCPC intracardiac lateral tunnel	81%	62%	54%	42%		
TCPC extracardiac lateral tunnel	6%	9%	15%	21%		
TCPC extracardiac conduit	4%	13%	12%	20%		
Tei index (by tissue Doppler)	0.57	0.60	0.62	0.65	<0.001*	0.012
Overall AV valve regurgitation					0.002†	0.010
None	32%	27.1%	26.7%	18.8%		
Mild	55%	57.5%	50.5%	55.6%		
Moderate	13%	14.9%	22.8%	25.6%		
Severe	0%	<1%	0%	0%		

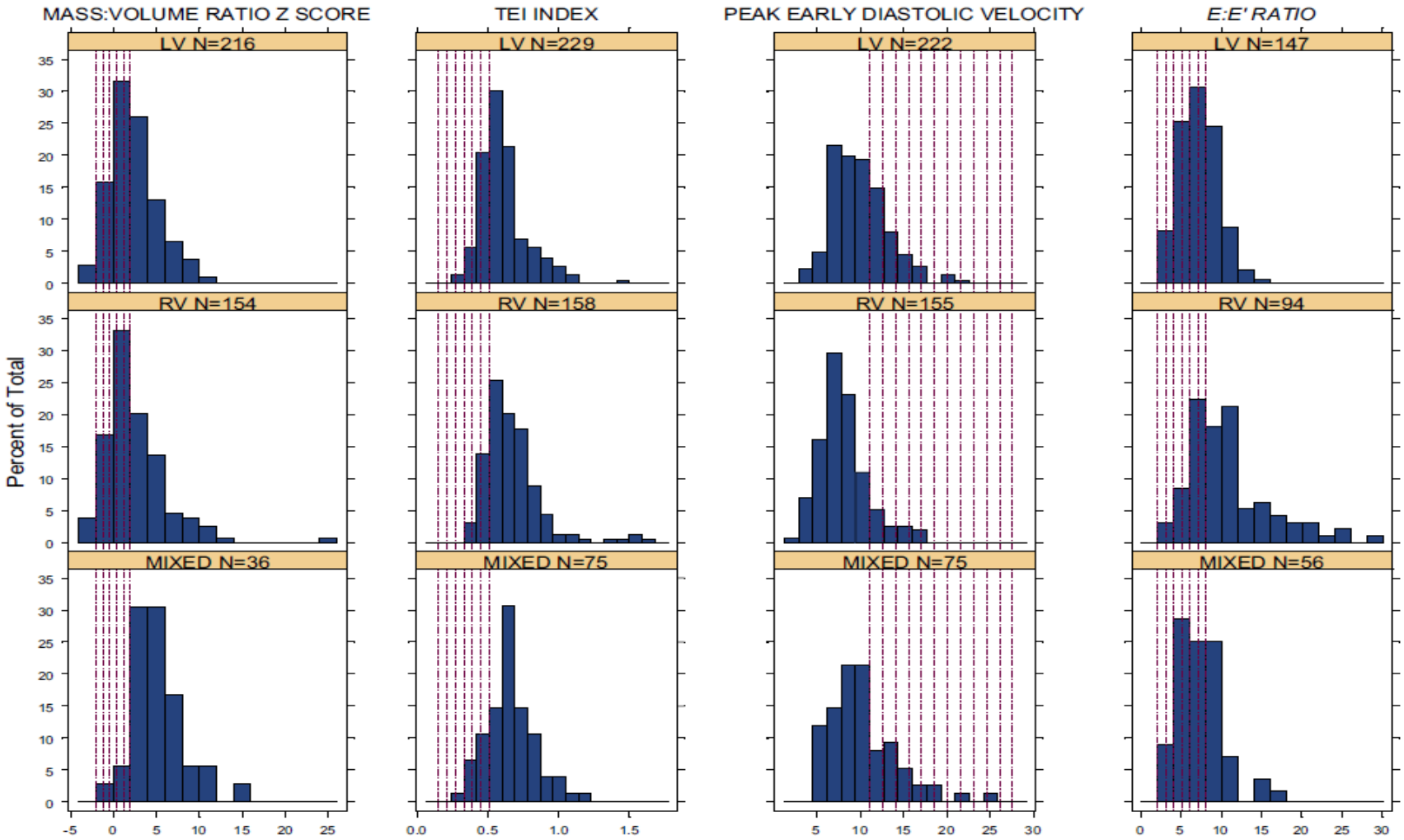
(Anderson, J Am Coll Cardiol 2008)

Fontan Cross-Sectional Study by Age at Enrollment – Cardiac Function

		Overall	<9 yrs	9 to <11 yrs	11 to <15 yrs	≥15 yrs	
Characteristic	n	Mean ± SD. Median. or %	Mean ± SD. Median. or %	Mean ± SD. Median. or %	Mean ± SD. Median. or %	Mean ± SD. Median. or %	p Value
Mass Z score	406	1.0 ± 2.3	0.7 ± 2.0	0.9 ± 2.3	0.8 ± 2.1	1.7 ± 2.7	0.011
Ejection fraction, %	414	59 ± 10	59 ± 10	60 ± 10	59 ± 11	57 ± 11	0.252
Mass/volume ratio, g/ml	406	1.21 ± 0.39	1.16 ± 0.41	1.20 ± 0.38	1.23 ± 0.38	1.26 ± 0.38	0.321
Mass/volume ratio Z score	406	2.65 ± 3.22	1.97 ± 3.06	2.41 ± 2.97	2.86 ± 3.15	3.49 ± 3.63	0.011
dP/dt_{ic}, mm Hg/s	449	1,125 (802, 1,700)†	1,257 (n = 115)	1,134 (n = 106)	1,114 (n = 134)	997 (n = 94)	0.027*
Tei index (by tissue Doppler)	462	0.64 ± 0.19	0.60 ± 0.17 (n = 117)	0.62 ± 0.14 (n = 99)	0.63 ± 0.17 (n = 144)	0.70 ± 0.24 (n = 102)	<0.001
Restrictive pattern present	344	52%	52%	54%	56%	44%	0.421
Diastolic dysfunction grade	327						0.438‡
Normal		28%	23%	27%	25%	38%	
Impaired relaxation		9%	12%	8%	9%	8%	
Pseudonormalization		41%	45%	47%	42%	29%	
Restrictive		22%	20%	18%	24%	26%	

(Anderson, J Am Coll Cardiol 2008)

Fontan Cross-Sectional Study by Ventricular morphology – Cardiac function



(Anderson, J Am Coll Cardiol 2008)

Fontan Cross-Sectional Study by Ventricular morphology -Cardiac function

Characteristic	LV Mean ± SD, Median, or %	RV Mean ± SD, Median, or %	Mixed Mean ± SD, Median, or %	p Value	Age-Adjusted p Value
Overall AV valve regurgitation				<0.001	<0.001
None	38%	12%	20%		
Mild	48%	69%	49%		
Moderate	15%	18%	31%		
Severe	0%	<1%	0%		
Semilunar valve regurgitation				0.004	0.001
None	58%	35%	58%		
Mild	34%	55%	32%		
Moderate	8%	10%	10%		

(Anderson, J Am Coll Cardiol 2008)

Fontan Cross-Sectional Study by Age at Enrollment – Arrhythmia related

		Overall	<9 yrs	9 to <11 yrs	11 to <15 yrs	≥15 yrs	
Characteristic	n	Mean ± SD, Median, or %	Mean ± SD, Median, or %	Mean ± SD, Median, or %	Mean ± SD, Median, or %	Mean ± SD, Median, or %	p Value
Predominant rhythm	518						0.255
Normal sinus rhythm		67%	63%	69%	71%	63%	
Atrial escape		9%	11%	10%	7%	9%	
Junctional escape		6%	9%	6%	5%	3%	
Paced		8%	10%	4%	9%	11%	
Other		11%	8%	12%	9%	15%	
Currently on pacemaker	546	13%	12%	12%	11%	20%	0.087
Serology							
Brain natriuretic peptide, pg/ml	510	13 (7, 26)†	11	11	14	17	0.020*

(Anderson, J Am Coll Cardiol 2008)

Arrhythmias in a Contemporary Fontan Cohort

Prevalence and Clinical Associations in a Multicenter Cross-Sectional Study

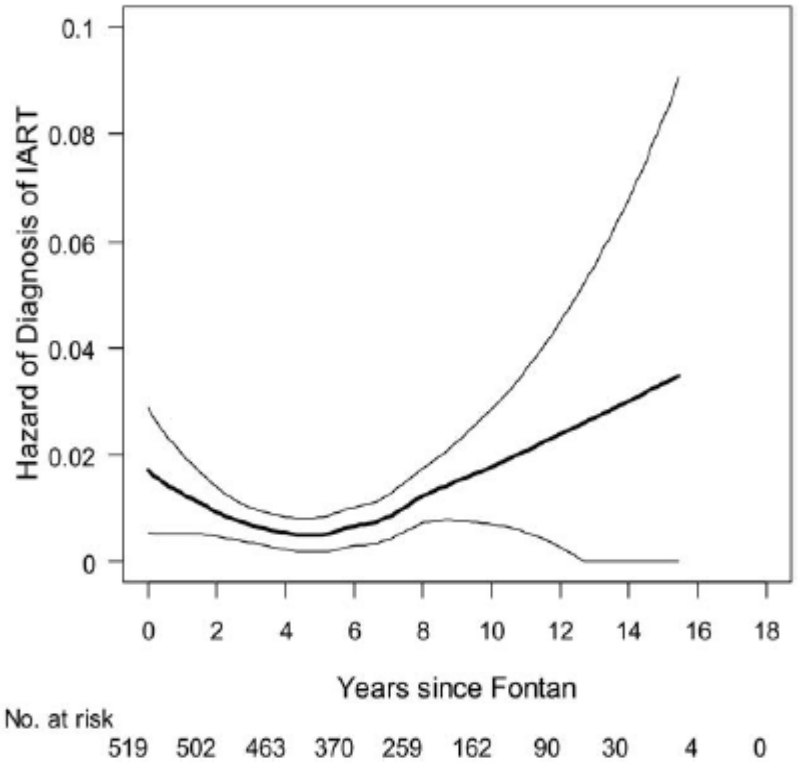


Figure 1 Hazard of IART Following the Fontan Operation, With 95% Confidence Bands

Date of diagnosis was missing for 1 patient, thus the number at risk initially is 519. IART = intra-atrial re-entrant tachycardia.

Table 3 Association of Anatomy and Function With History of IART

Variable	n	History of IART	n	No History of IART	p Value*
Anatomic diagnosis	38		482		0.24
Single LV: DILV and TA		47%		36%	
Single RV: DIRV; MA and HLHS		13%		28%	
SV, unbalanced AV canal defect		3%		4%	
Other		26%		24%	
SV, heterotaxia syndrome		11%		7%	
Ventricular morphology	38		482		0.13
Left ventricular		61%		49%	
Right ventricular		18%		34%	
Mixed		21%		17%	
L loop anatomy	38	32%	482	18%	0.05
AV valve regurgitation	37	78%		74%	0.70
AV valve regurgitation severity	37		465		0.38
None		22%		27%	
Mild		54%		54%	
Moderate/severe		24%		19%	
Semilunar valve regurgitation	22	55%	279	49%	0.66
Semilunar valve regurgitation severity	22		279		0.94
None		46%		51%	
Mild		50%		39%	
Moderate		5%		9%	
Echocardiographic ejection fraction, %	27	58.1 ± 10.7	366	58.3 ± 10.4	.95
Echocardiographic ejection fraction z-score	27	−1.0 ± 2.1	366	−0.9 ± 2.0	.94

Stephenson, JACC 2010

Table 4 Multivariable Cox Regression Model for IART (n = 464)*

Cox Regression Model	Hazard Ratio	95% CI	p Value
CHQ physical summary score	1.23 per 5-U decrease	1.09–1.37	<0.001
Predominant rhythm			0.002
Paced vs. atrial-based	4.01	1.84–8.75	<0.001
Paced vs. junctional escape	4.85	0.61–38.70	0.14
Atrial-based vs. junctional escape	1.21	0.16–9.07	0.85
Type of Fontan operation			0.04
Atriopulmonary connection	—	—	—
Intracardiac lateral tunnel	0.35	0.17–0.75	0.007
Extracardiac lateral tunnel	0.75	0.20–2.87	0.68
Extracardiac conduit	0.22	0.03–1.77	0.16

*The data of 56 of 520 subjects were excluded from the model: 11 patients with "other" type of Fontan, 14 with other/unknown type of predominant rhythm 30 with missing CHQ score, and 1 with unknown date of discharge after Fontan.

CHQ = Child Health Questionnaire; CI = confidence interval; IART = intra-atrial re-entrant tachycardia.

Stephenson, JACC 2010

- Overall prevalence of IART was lower in this cohort (7.3%) than previously reported(16-22%).
- Lower functional status, an AP connection, and paced rhythm were determined to be independently associated with development of IART after Fontan
- Cardiac anatomy and resting HR, not asso with IART

Stephenson, JACC 2010

Fontan Cross-Sectional Study by Age at Enrollment – Exercise Capacity

Characteristic	n	Overall	<9 yrs	9 to <11 yrs	11 to <15 yrs	≥15 yrs	p Value
		Mean ± SD, Median, or %	Mean ± SD, Median, or %	Mean ± SD, Median, or %	Mean ± SD, Median, or %	Mean ± SD, Median, or %	
Exercise performance measures							
n		412	68	95	152	97	
Peak VO_2, ml/kg/min	403	26 ± 7	27 ± 8 (n = 65)	28 ± 7 (n = 94)	26 ± 6 (n = 148)	25 ± 7 (n = 96)	0.028
Percent predicted peak VO_2	403	65 ± 16	67 ± 19	68 ± 17	65 ± 15	59 ± 14	<0.001
Peak VO_2 consumption at AT, ml/kg/min	317	19 ± 6	24 ± 8 (n = 35)	20 ± 7 (n = 65)	19 ± 6 (n = 131)	16 ± 5 (n = 86)	<0.001
Percent predicted VAT	317	78 ± 25	95 ± 30	82 ± 26	77 ± 22	69 ± 20	<0.001
Maximum heart rate, beats/min	405	154 ± 23	152 ± 22 (n = 64)	156 ± 24 (n = 95)	157 ± 21 (n = 150)	150 ± 26 (n = 96)	0.122

(Anderson, J Am Coll Cardiol 2008)

Long-term cardiopulmonary exercise capacity after modified Fontan operation

Stanislav Ovroutski [a,*], Peter Ewert [a], Oliver Miera [a], Vladimir Alexi-Meskishvili [b], Bjorn Peters [a], Roland Hetzer [b], Felix Berger [a]

Table 1

Preoperative and intra-operative data in children and adults.

Data	Children, $n = 28$	Adults, $n = 15$	p value
Gender (m/w, n)	14/15	8/7	n.s.
LV/RV systemic morphology (n)	22/6	12/3	n.s.
Previous BCPS (n)	26	9	n.s.
Aorto-pulmonary shunt	16	2	0.023
Lateral tunnel/extracardiac Fontan (n)	13/15	9/6	n.s.

BCPS: bidirectional cavopulmonary shunt; LV: left ventricle; and RV: right ventricle.

Ovroutski, et al. European Journal of Cardio-thoracic Surgery, 2010

- Spirometry at least twice with median age 14(7–43)
- Median time interval of 4.6(1.1–10.4) years between early and late testing

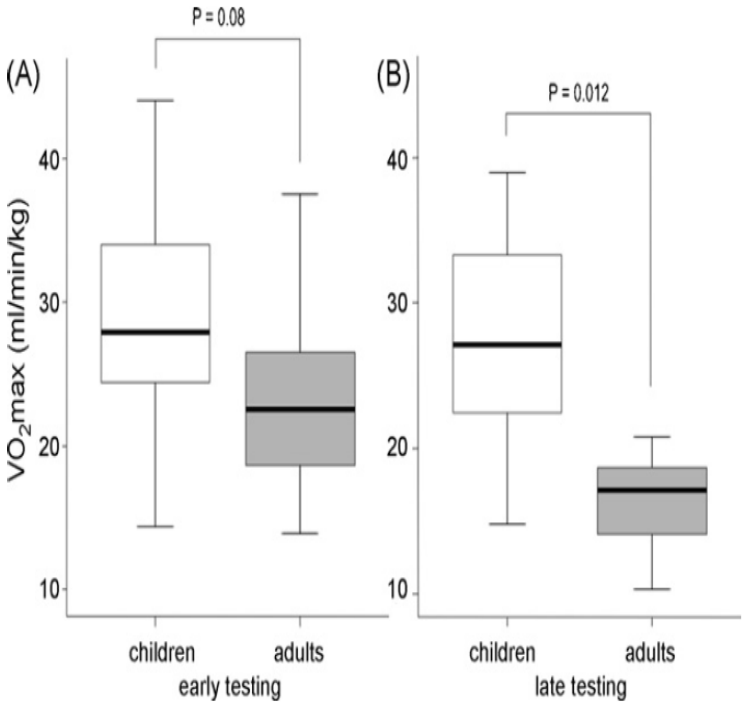


Fig. 1. Cardiopulmonary capacity (VO_{2max}) early and late postoperatively in children and adults. The box-plot diagram shows the early (A) and late (B) postoperative cardiopulmonary capacity (VO_{2max}) in the comparison between children and adults. The differences are clear, especially late postoperatively, where they are statistically highly significant.

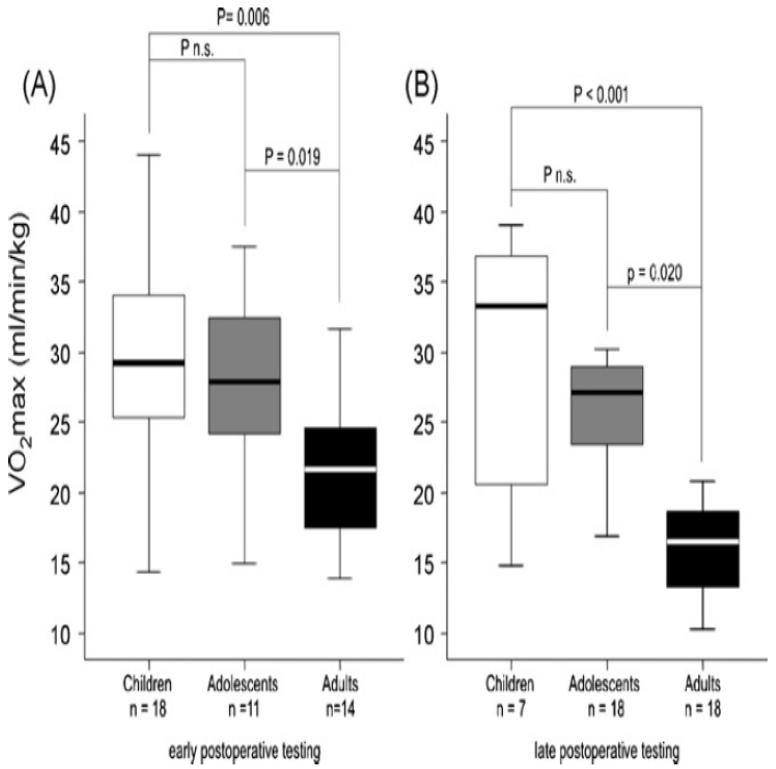
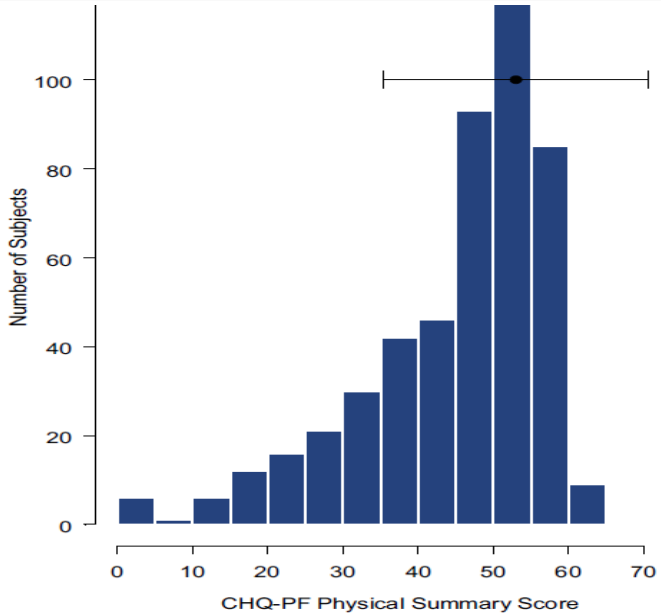


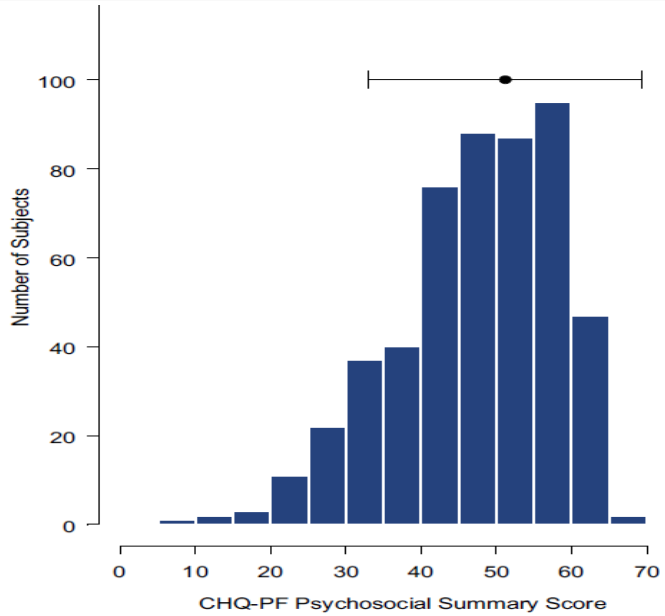
Fig. 3. The box-plot diagram shows the early (A) and late (B) postoperative cardiopulmonary capacity (VO_{2max}) in the comparison between children, adolescents and adults.

Ovroutski, et al. European Journal of Cardio-thoracic Surgery, 2010

Neurodevelopmental Outcome

Characteristic	n	Overall	<9 yrs	9 to <11 yrs	11 to <15 yrs	≥15 yrs	p Value
		Mean ± SD, Median, or %	Mean ± SD, Median, or %	Mean ± SD, Median, or %	Mean ± SD, Median, or %	Mean ± SD, Median, or %	
Measures of functional status							
CHQ-PF Physical Summary score	511	45.3 ± 11.9	45.7 ± 12.1	45.8 ± 10.7	45.4 ± 12.6	44.1 ± 11.7	0.689
CHQ-PF Psychosocial Summary score	511	47.2 ± 10.8	47.9 ± 10.6	47.2 ± 11.1	45.5 ± 10.9	49.1 ± 10.5	0.052





(Anderson, J Am Coll Cardiol 2008)

Cognitive Developmental Outcome

- 133 Fontan
  - Mean full scale IQ lower than normal (95.7±17.4,86)
  - 7.8%(18), below the threshold for mental retardation
  - Independent variable – HLHS
- No significant depression in IQ in Fontan including HLHS
- HLHS(93.8±7.3) significant lower scores than non-HLHS(107.0±7.0)

Wernovsky, et al Boston/philadephia, 2000

Goldberg, et al. Michigan, 2000

Thrombotic Complication

- Low-flow state, hypercoagulable state, atrial arrhythmia, suture line, scarring, clotting factor loss
- High as 20-30%, TTE, 592 Fontan
- Freedom from thrombus 92% at 1year, 90% at 3year, 82% at 10year
- No difference in AP & lateral, fenestration or not.
- Not clear how to screen, prevention of thromboembolic phenomenon.

Protein Losing Enteropathy

- Devastating Complication, respond poorly to present treatment protocol.
- Prevalence of 2.5-24% with post onset 5-year survival rate of approximately 46-59%
- Risk factors for development of PLE
- High systemic venous pressure(?)
- RV anatomy (?) Powel et al. 416 Fontan, Op 1973-91)
- Postop(Longer CP bypass time, prolonged CT drainage, ICU stay, PO renal failure)
- Preop(low pulmonary vascular compliance)

Summary I

- Gradual attrition occurs predominantly from thromboembolic, HF-related and sudden death.
- Ventricular systolic function and functional health status were within normal range in the majority of subjects.
- Ventricular function and valvular function were negatively associated with RV morphology.

Summary II

- Continued follow-up of Fontan subjects will determine whether functional health status is eventually related to measures of ventricular diastolic function.
- Effective strategies to preserve ventricular and valvular function, particularly for patients with RV morphology, are needed.