

openheart Survival in patients with univentricular hearts: the impact of right versus left ventricular morphology

Gunnar Erikssen,¹ Jamil Aboulhosn,² Jeannette Lin,² Knut Liestøl,³ Mette E Estensen,¹ Ola Gjesdal,¹ Helge Skulstad,⁴ Gaute Døhlen,⁵ Harald Lauritz Lindberg⁶

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¹ACHD Unit, Department of Cardiology, Oslo University Hospital Rikshospitalet, Oslo, Norway

²Ahmanson/UCLA Adult Congenital Heart Disease Center, UCLA Medical Plaza, Los Angeles, California, USA

³Department of Informatics, University of Oslo, Oslo, Norway

⁴Faculty of Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

⁵Department of Pediatric Cardiology, Oslo University Hospital, Oslo, Norway

⁶Department of Thoracic Surgery, Oslo University Hospital, Oslo, Norway

Correspondence to

Dr Gunnar Erikssen; gunnar.erikssen@yahoo.com

ABSTRACT

Objective Patients with univentricular hearts (UVH) have high mortality despite modern treatment, and better methods to identify patients at highest risk are needed. We wanted to improve risk stratification in patients with UVH by focusing on the prognostic significance of single right versus single left ventricular morphology (SRV vs SLV).

Methods All 395 patients with UVH operated at our centre were prospectively included from 1972 to 2016 (195 SRV, 166 SLV, 34 mixed or indeterminate ventricular morphology). Diagnoses, UVH morphology, types of all operations and time and causes of death or heart transplantation (HTX) were recorded. The primary endpoint was death or HTX.

Results Among the 111 non-Fontan patients, 88 died (SRV 62 vs SLV 20; $p < 0.0001$), 32 due to heart failure (SRV 23 vs SLV 5; $p = 0.0012$). Twenty-five years of cumulative SRV versus SLV survival among the 284 Fontan patients (41 deaths/HTX) was 66.9% vs 87.9% ($p = 0.0027$), partly explained by more deaths/HTX due to heart failure among patients with SRV ($p = 0.0006$). Survival in patients with SRV with and without hypoplastic left heart syndrome (HLHS) was similar. SRV versus SLV was a strong predictor of death/HTX in multivariable proportional hazards analyses (RR 3.3, 95% CI 1.6 to 6.6).

Conclusion SRV versus SLV is a strong short-term and long-term predictor of survival among patients with UVH, mainly explained by higher rates of death/HTX due to heart failure in the SRV group. Our findings apply to patients with SRV both with and without HLHS.

INTRODUCTION

Patients with univentricular hearts (UVH) selected for surgical intervention typically undergo a sequence of operations usually culminating in the establishment of Fontan circulation. Substantial advances in surgical techniques and other treatment modalities^{1 2} have improved survival considerably.³ Still, patients with UVH—currently accounting for about 20% of patients with complex heart defects (CHD)—have the highest mortality,⁴ and mortality is high both around initial treatment and during long-term follow-up. Thus, there is a need for

Summary

What is already known about this subject?

- ▶ One previous study showed that single right ventricular morphology (SRV) versus single left ventricular morphology (SLV) was a predictor of death or heart transplantation (HTX) following initial surgical palliation in patients with univentricular heart (UVH), but conflicting evidence exists on the prognostic significance of SRV versus SLV after establishment of Fontan circulation.

What does this study add?

- ▶ SRV versus SLV was a strong predictor of death or HTX in patients with UVH both prior to and after Fontan surgery, apparently mainly driven by increased risk of death or HTX due to heart failure among patients with SRV.
- ▶ The increased risk includes patients with SRV with hypoplastic left heart syndrome, and a broader group of patients with UVH with SRV.

How might this impact on clinical practice?

- ▶ Ventricular morphology should be included as an important risk factor during the initial evaluation for surgical treatment of patients with UVH.
- ▶ After Fontan surgery, there should be particular emphasis in patients with SRV on treatment of modifiable risk factors for development of heart failure, like volume or pressure overload.

preoperative risk stratification algorithms that may discriminate high and low-risk patients. Age at operation, gender, cardiac anatomy and cardiac function have been associated with long-term mortality.^{5 6} Further, in a recent Editorial,^{1 7} Gersony hypothesised higher long-term mortality due to heart failure among patients with single right ventricular morphology (SRV) compared with single left ventricular morphology (SLV). However, conflicting evidence exists on the prognostic significance of SRV versus SLV.^{2 3 6–9} The present study has two aims: to study the long and short-term prognostic significance of SRV versus SLV based on

prospective data from 395 patients with UVH operated at Oslo University Hospital (OUS), and further to study potential differences in the patterns of fatal complications.

METHODS

Materials

The study was conducted at the Departments of Thoracic Surgery and Pediatric Cardiology, and at the Unit of Adult Congenital Heart Disease, Department of Cardiology, OUS, Rikshospitalet. All operations on patients with UVH, including heart transplantations (HTX), were registered prospectively in the DATACOR database from 5 May 1972 to 31 December 2016, along with dates and causes of death as described previously.⁴ No patients were lost to follow-up.

Data handling was facilitated by using each patient's unique 11-digit social security number, which includes individual birth date. CHD diagnoses were based on International Classification of Diseases (ICD)-9 until 1998, and ICD-10 thereafter. The dates and types of all operations were recorded, and a maximum of three diagnoses were given. In cases where the ICD was inadequate, diagnoses were adjusted according to van Mierop.¹⁰

All patients with UVH who underwent one or more heart operations and had their first operation at Rikshospitalet were included. Between 1971 and 2003, eighty per cent of all CHD surgical procedures in Norway were performed at this institution. Since 2003, all CHD surgery in Norway has been performed at Rikshospitalet. Between 1987 and 1998, fifty-one patients with hypoplastic left heart syndrome (HLHS) from Norway had their Fontan surgery in the USA or Switzerland (25 survivors) due to government regulations.¹¹ These patients have not been included.

Definitions

UVHs were retrospectively classified as having either a single dominant morphologically right ventricle (SRV) and a rudimentary left ventricle, a single dominant morphologically left ventricle (SLV) and a rudimentary right ventricle, or a functionally single ventricle with mixed or indeterminate ventricular morphology (MIX) according to a recognised nomenclature.¹² The diagnoses were based on echocardiographic studies, MRI and invasive studies.

A bidirectional cavopulmonary connection (BCPC) involves rerouting the superior vena cava into the pulmonary artery. During a Fontan procedure, systemic venous return from the upper and lower body is diverted to the pulmonary artery without passing through the ventricle(s). We divided the Fontan procedures among our patients in three main groups: (1) extracardiac total cavopulmonary connection¹³; (2) intracardiac total cavopulmonary connection (lateral tunnel)¹⁴; and (3) others, including variants of the classical atriopulmonary Fontan.¹⁵ The first palliative shunt operation in our

material was performed on 22 May 1972, and the first Fontan procedure on 5 May 1979.

The term 'failing Fontan' represents a variety of pathophysiologies that may develop secondary to the heart defect and mode of correction, especially low cardiac output and elevated central venous pressure.^{16,17} End-stage Fontan failure is refractory to optimised medical therapy.

The primary endpoint in the survival analyses was death or HTX. Depending on the analysis, the starting point was the date of birth or the date of the Fontan operation. 'Early mortality' includes all deaths occurring 30 days or less after surgery.

Statistical analyses

We used Kaplan-Meier analyses to study survival after birth and after the Fontan procedure. The log-rank test (Mantel-Cox) was used to test for differences in survival.

Proportional hazards (Cox) analyses were used to explore the prognostic significance of right versus left ventricular morphology after correction for possible confounders (gender, Fontan age, Fontan era and Fontan method). Variables that were found to be significantly associated with outcome in univariable analyses were included in the multivariable analysis. The proportional hazards assumption was adequately fulfilled for all covariables.

Two-sample t-tests were used when comparing clinical variables among survivors.

P values (two sided) <0.05 were considered significant. The statistical package StatView V.5.0 was used for analyses.

RESULTS

Surgical treatment

In total, 395 patients with UVH were included (figure 1). All had at least one operation, and total number of operations was 997. The number of patients with SLV was 166 (42.0%), SRV 195 (49.4%) and MIX 34 (8.6%). There were substantial SLV versus SRV differences in types of initial surgical procedures, reflecting differences in UVH diagnostic profiles (table 1). Numbers of women versus men were 177 vs 218 (p=0.022). Median age at initial surgery was 15 vs 6 days in patients with SLV versus SRV (p<0.0001).

Fontan circulation was established in 284/395 patients (71.9%); 250 after BCPC and 34 without previous BCPC, and in a larger proportion of patients with SLV than SRV (138/166 (83.1%) vs 120/195 (61.5%), p<0.0001). A total of 219/284 patients (77.4%) had their Fontan surgery before 5 years of age. Figure 2 shows the distribution of various Fontan methods in different eras. Fenestrations were created in 99 patients (34.1%).

Age at Fontan surgery among patients with SLV and SRV was similar, as were proportions of classical, lateral tunnel and extracardiac conduit Fontan, patients with fenestration and patients who had BCPC before Fontan. However, the percentage of patients who had palliative

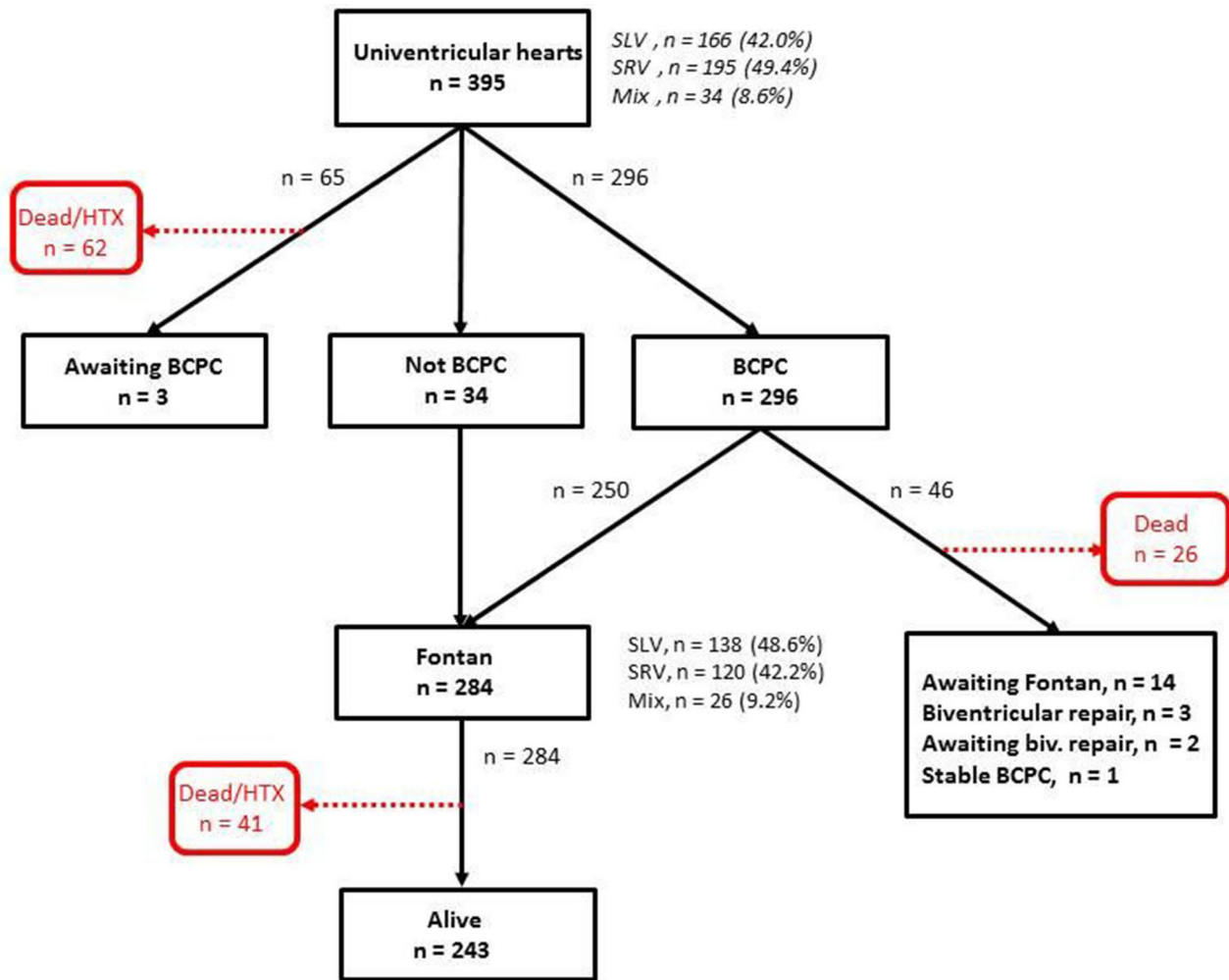


Figure 1 Treatment history of 395 study patients with univentricular hearts. BCPC, bidirectional cavopulmonary connection; HTX, heart transplantation; Mix, mixed or indeterminate ventricular morphology; SLV, single left ventricular morphology; SRV, single right ventricular morphology.

surgery before BCPC was larger in the SRV group than in the SLV group ($p=0.0002$) (table 2). Proportions of female versus male patients having Fontan surgery were similar to the female versus male ratio in the entire UVH population.

Reoperations and transcatheter interventions

Among the 284 Fontan patients, eight underwent reoperation within 30 days after the Fontan procedure. Forty (14.1%) patients had different types of late surgical revisions: 18 had conversion to extracardiac conduit or lateral tunnel (1 patient), 9 had opening/closure of fenestrations, 6 had valve surgery, 3 had intraventricular resections and 4 had other types of surgical procedures. There was no difference between SRV and SLV with respect to proportions of patients undergoing Fontan conversion ($p=0.82$; details not shown).

Forty-three (15.1%) Fontan patients had transcatheter fenestration closures, 66 (23.2%) had balloon dilations with or without stents in the pulmonary artery or in the Fontan conduits, and 53 (18.7%) had closures of veno-venous or arteriovenous collaterals and 40 (14.1%) had

balloon dilations with or without stents in the descending aorta. Among these 40 patients, 36 had SRV ($p<0.0001$); all patients with HLHS. Otherwise, no SRV versus SLV differences in proportions of patients having transcatheter procedures were found. In addition, 38 patients (13.4%) had permanent pacemakers, 1 patient (0.3%) had a defibrillator and 15 (5.3%) had radiofrequency ablations due to arrhythmias.

Survival

All patients with UVH

A total of 118 patients (29.9%) died during follow-up, and 13 patients (3.3%) underwent HTX (2 died after HTX). Accordingly, 129 patients died or had HTX. Figure 3 shows a markedly better survival among patients with SLV than among SRV. Twenty-five years of cumulative SLV versus SRV survival was 74.9% vs 42.5% ($p<0.0001$), and 69.1% in the group with MIX (figure 3). Among patients with atrioventricular septal defect, long-term survival was similar regardless of right or left ventricular dominance. Otherwise, survival within all SLV diagnostic subgroups (table 1) was significantly higher than mean SRV survival,

Table 1 Demographic data, initial surgical procedures and primary UVH diagnoses

	SLV	SRV	MIX	Total
Female, n (%)	84 (50.6)	82 (42.1)	11 (32.4)	177 (44.8)
Initial surgical procedures				
BAP	38	19	3	60
BCPC	28	9	10	47
Shunt	83	41	16	140
Norwood I	6	123	4	133
Fontan	5	2	1	8
Other operations	6	1	0	7
Total	166	195	34	395
Primary UVH diagnoses				
TA	72	0	0	72
HLHS	0	121	0	121
DILV	40	0	3	43
DORV	0	28	4	32
AVSD	6	12	13	31
PA-IVS	32	0	1	33
Misc	16	34	13	63
Total	166	195	34	395

AVSD, atrioventricular septal defect; BAP, banding of the pulmonary artery; BCPC, bidirectional cavopulmonary connection; DILV, double inlet left ventricle; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; MIX, mixed or indeterminate ventricular morphology; Misc, miscellaneous heart defects; PA-IVS, pulmonary atresia with intact ventricular septum; SLV, single left ventricular morphology; SRV, single right ventricular morphology; Shunt, central aorticopulmonary shunt (Waterston, Blalock-Taussig, etc.); TA, tricuspid atresia; UVH, univentricular heart.

and survival within all SRV subgroups was significantly lower than mean SLV survival (online supplementary figure 1).

Non-Fontan patients

Among the 111/395 patients (28.1%) who did not undergo or were awaiting Fontan operation, the majority had SRV (table 3). This difference was mainly due to higher mortality in the SRV group (SRV 62/195 (31.8%) vs SLV 21/166 (12.7%), $p<0.0001$).

SRV mortality was higher than SLV mortality both among patients with HLHS (40/121 (33.1%); $p<0.0001$) and among non-HLHS patients (22/74 (29.7%); $p=0.001$). The dominant cause of death among non-Fontan patients was heart failure (SLV 5, SRV 23; $p=0.0012$).

Fontan patients

Among the 284 Fontan patients, 41 died (29 patients) or had HTX (12 patients). Sixteen patients (5.6%) died within 30 days after the operation. Median follow-up time among Fontan survivors was 11.0 years (mean 11.4 years,

SD 7.3 years). Twenty-five years of cumulative survival was significantly higher among patients with SLV compared with patients with SRV (87.9% vs 66.9%, $p=0.0027$), even when disregarding early mortality (92.5% vs 70.8, $p=0.0005$) (online supplementary figure 2). Twenty-five years of cumulative survival among patients with MIX was 91.6% (details not shown).

Survival among Fontan patients with SLV was significantly higher than survival among patients with SRV both with and without HLHS (figure 4).

Details on causes of death and HTX among Fontan patients are shown in table 4. In total, one patient with SLV versus 11 patients with SRV died or had HTX due to heart failure ($p=0.0006$), and one had mixed or indeterminate morphology. Nine of these patients had systolic heart failure, three combined systolic heart failure and significant valvar disease, and one systolic heart failure and intractable arrhythmias. Otherwise, there were no SRV versus SLV differences in causes of death or HTX.

Sequential changes in survival

Among the Fontan patients, there was a gradual improvement in survival from the beginning to the end of the study period (online supplementary figure 3, panel A). However, most of the differences in survival between eras were attributable to differences in early mortality (online supplementary figure 3, panel B).

Multivariable analysis

Since survival among patients with SLV and MIX was almost identical, these groups were merged in the proportional hazards analyses. Fontan era was treated as a dichotomous variable (1979–2000 vs 2001–2016). In univariable analyses including ventricular morphology (SRV vs SLV+MIX), Fontan era, Fontan age, gender and Fontan type, only SRV versus SLV+MIX and Fontan era were significantly associated with outcome. In the multivariable analysis both these variables were strong predictors of death or HTX (table 5). In a similar multivariable analysis excluding patients with MIX ($n=26$), SRV versus SLV was a strong predictor of death or HTX (RR=3.3; 95% CI 1.6 to 6.6).

DISCUSSION

In the present prospective study we explore predictors of survival in patients with UVH throughout the surgical treatment process and beyond the establishment of Fontan circulation. Our main findings are that SRV versus SLV is a strong predictor of increased mortality or HTX both before and after Fontan surgery, and that the SRV versus SLV differences are mainly driven by differences in mortality or HTX due to heart failure. Moreover, our findings apply to patients with SRV both with and without HLHS.

Previous studies

The prognostic significance of SRV versus SLV following initial surgical palliation in patients with UVH has been

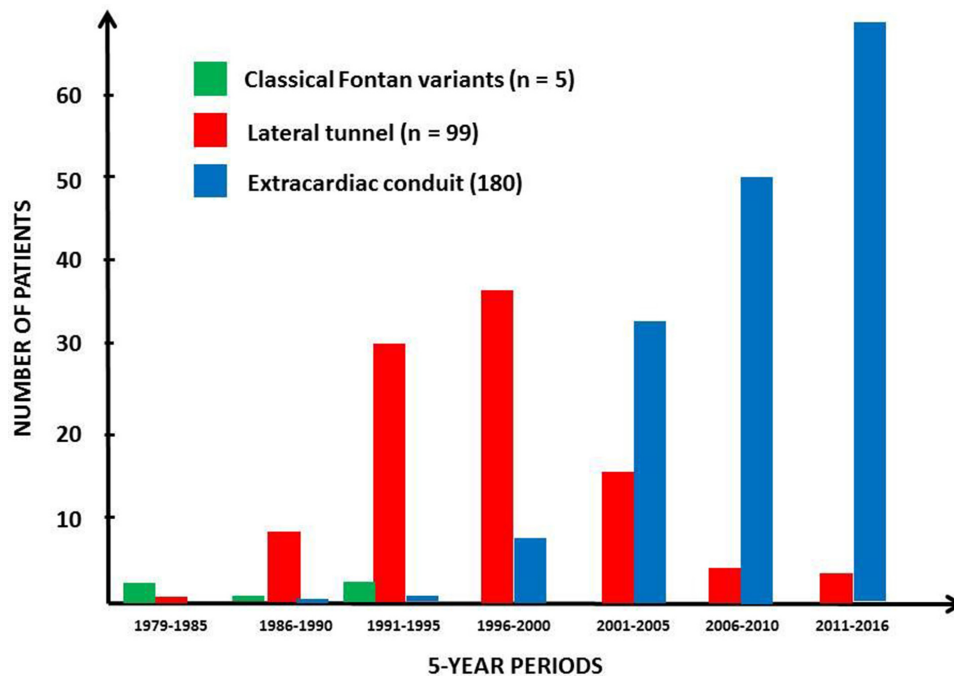


Figure 2 Numbers and proportions of different Fontan procedures in different eras.

explored in one large previous study.⁸ In that study, including 499 patients born in Australia between 1990 and 2008, SRV was found to be a strong predictor of mortality during the first years of life before BCPC and Fontan surgery—similar to our findings. However, that study did not show that SRV was a predictor of mortality after establishment of BCPC.

In a study from the Mayo Clinic including 1052 Fontan patients undergoing operation between 1973 and 2012, differences in ventricular morphology did not predict differences in long-term survival.⁶ In two subsequent studies from Australia and New Zealand, HLHS was a significant predictor of long-term Fontan failure,^{3,9} but not of death. In a recent study from Spain including 91 Fontan patients operated in 1995–2013,² SRV was a significant predictor of all-cause mortality.

In summary, previous studies have not unambiguously clarified the relevance of SRV versus SLV as a predictor of mortality in UVH prior to and after Fontan operations. However, according to our data, SRV versus SLV was a strong predictor of mortality through all stages of surgical correction in patients with UVH.

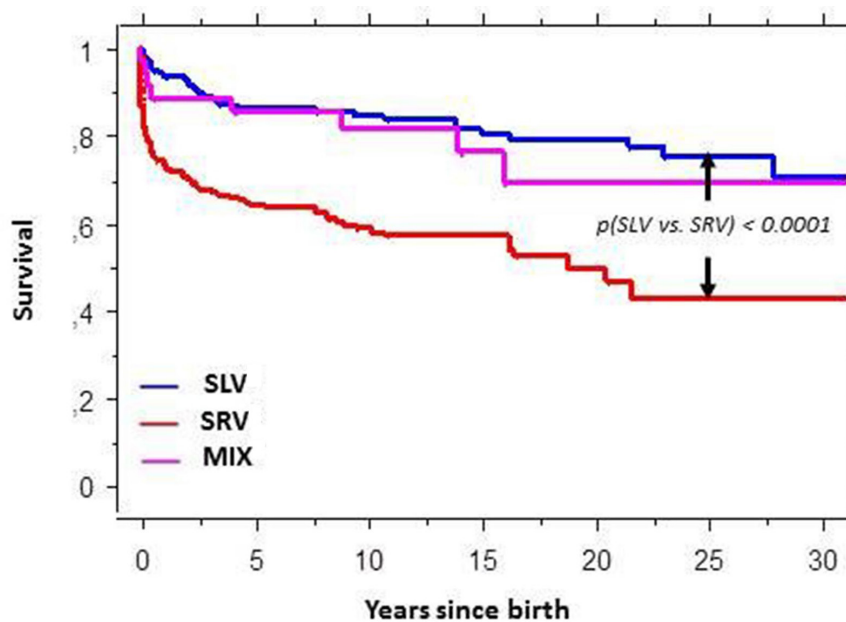
Selection issues

Data on the true birth incidence of different CHDs compared with the proportions of various types of CHD given in different studies suggest differences in selection of patients. However, the use of different diagnostic classification systems makes comparisons among studies difficult. Nevertheless, according to a meta-analysis based on 44 published studies on the birth incidence of CHD (median CHD incidence 1.0%), the ratio between

Table 2 Demographic data and surgical procedures in Fontan patients

	SLV (n=138)	SRV (n=120)	MIX (n=26)	Total (n=284)
Female (%)	71 (51.4)	45 (37.5)	9 (34.6)	125 (44.0)
BCPC ^a before Fontan (%)	118 (85.5)	108 (90.0)	24 (92.3)	250 (88.0)
Palliation before BCPC (%)	88 (63.8)	101 (84.2)	13 (50.0)	202 (71.1)
Fontan age (median, years)	3.3	3.2	4.7	3.4
Classical Fontan (%)	3 (2.1)	2 (1.7)	0 (0.0)	5 (1.8)
Lateral tunnel (%)	53 (38.4)	36 (30.0)	10 (38.5)	99 (34.9)
Extracardiac conduit (%)	82 (59.4)	82 (68.3)	16 (61.5)	180 (63.4)
Fenestration (%)	46 (33.3)	45 (37.5)	8 (30.8)	99 (34.9)

BCPC, bidirectional cavopulmonary connection; MIX, mixed or indeterminate ventricular morphology; SLV, single left ventricular morphology; SRV, single right ventricular morphology.



# at risk (SLV):	166	105	46	10
# at risk (SRV):	195	67	16	8
# at risk (MIX):	34	22	6	2

Figure 3 Cumulative survival in patients with univentricular hearts (UVH). MIX, mixed or indeterminate ventricular morphology; SLV, single left ventricular morphology; SRV, single right ventricular morphology; #, number of patients.

the median birth incidence of HLHS (all morphologically SRV) and the median birth incidence of tricuspid atresia (TA; virtually all morphologically SLV) was about 2.5.¹⁸ In our study, the initial ‘HLHS/TA ratio’ was 1.6, indicating that some selection in favour of patients with TA had already taken place. At the time of Fontan

surgery, this ratio was reduced to 1.1 because of high pre-Fontan mortality in patients with SRV. In the previously mentioned Fontan studies, the HLHS/TA ratios were as low as 0.2 (7), 0.1 (6), 0.3 (3) and 0.6 (2), respectively. Accordingly, a much higher proportion of patients with SRV were included in our study compared with the

Table 3 Causes of death or HTX among the 111 non-Fontan patients

	SLV (n= 28)	SRV (n=75)	MIX (n=8)	Total (n=111)
Heart failure*	5	23	4	32
Postoperative complications†	3	13	2	18
Thrombosis‡	2	9	0	11
Pulmonary vascular disease§	4	6	0	10
Sudden death¶	2	8	0	10
Infection**	3	2	0	5
Bleeding††	1	1	0	2
Total	20	62	6	88

*Myocardial and/or valvar failure.

†Various complications within 30 days of last surgery.

‡Shunt thrombosis or thrombosis in Fontan circuit, myocardial infarction, stroke.

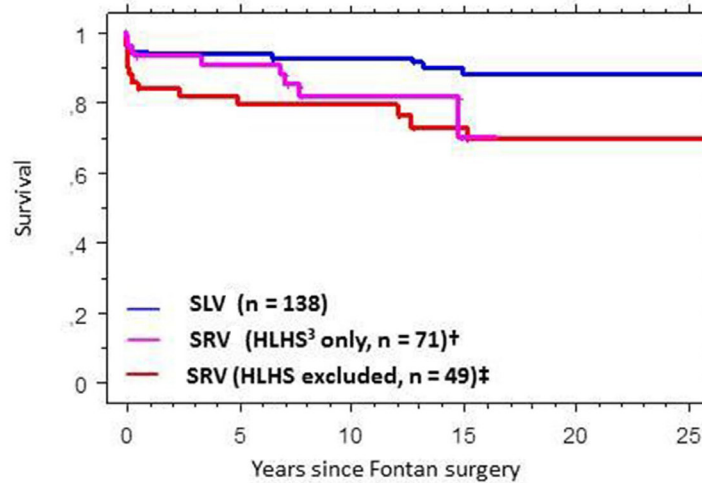
§Underdeveloped pulmonary vessels and/or high pulmonary vascular resistance.

¶Death occurring within minutes from any cause, including malignant tachyarrhythmias.

**Pneumonia, sepsis, gastroenteritis.

††Cerebral hemorrhage, pulmonary hemorrhage.

HTX, heart transplantation; MIX, mixed or indeterminate ventricular morphology; SLV, single left ventricular morphology; SRV, single right ventricular morphology.



# at risk (SLV):	138	102	81	53	29	10
# at risk (SRV, HLHS only):	71	41	20	7	0	0
# at risk (SRV, HLHS excluded):	49	37	27	20	6	1

Figure 4 Cumulative survival in Fontan patients with single left ventricular morphology versus single right ventricular morphology with and without hypoplastic left heart syndrome. HLHS, hypoplastic left heart syndrome; SLV, single left ventricular morphology; SRV, single right ventricular morphology; #, number of patients. [†]p(SLV vs SRV; HLHS only)=0.034. [‡]p(SLV vs SRV; HLHS excluded)=0.0018.

other studies. This indicates a substantial selection based on ventricular morphology prior to Fontan surgery in the other studies. In the study by d’Udekem and coworkers,⁸ the HLHS/TA ratio was similar to our data. However, only 209/383 (54.7%) of the BCPC patients underwent Fontan surgery compared with 250/284 (84.4%) in our study.

In summary, differences in patient selection and treatment routines make comparisons among Fontan studies difficult. Our patient population had an HLHS/TA ratio that was close to the birth incidence of these heart defects. Consequently, our study material may provide

more representative estimates of the prognostic impact of ventricular morphology in Fontan patients than previous studies.

Physiological considerations

In a study of Fontan patients operated in 2005–2013, ventricular stress–strain relationship in patients with SRV suggested heart failure, in part explaining unfavourable outcomes in Fontan patients with RV morphology.¹⁹ Echocardiographic and MR studies have demonstrated reduced strain rate and abnormal contraction pattern in SRVs of patients with transposition of the great arteries

Table 4 Causes of death or HTX among the 284 Fontan patients

	SLV (n=138)	SRV (n=120)	MIX (n=26)	Total (n=284)
Postoperative complications*	7	7	1	15
Heart failure [†]	1	11	1	13
Sudden death [‡]	1	3	0	4
Failed Fontan [§]	3	1	0	4
Infection [¶]	2	1	0	3
Thrombosis**	1	1	0	2
Total	15	24	2	41

*Various complications within 30 days of last surgery.

[†]Myocardial and/or valvar failure.

[‡]Death occurring within minutes from any cause, including malignant tachyarrhythmias.

[§]See Definitions.

[¶]Pneumonia, sepsis, gastroenteritis.

**Shunt thrombosis or thrombosis in Fontan circuit, myocardial infarction, stroke.

HTX, heart transplantation; MIX, mixed or indeterminate ventricular morphology; SLV, single left ventricular morphology; SRV, single right ventricular morphology.

Table 5 Proportional hazards analysis for death or heart transplantation in Fontan patients

Covariables	Univariable analyses		Multivariable analysis	
	RR (95% CI)	P values	RR (95% CI)	P values
SRV* versus SLV+MIX	2.6 (1.4 to 5.0)	0.0041	2.9 (1.6 to 5.9)	0.0010
Intracardiac versus extracardiac Fontan	1.8 (0.9 to 3.5)	0.083		
Fontan era: 1979–2000 vs 2001–2016	2.7 (1.3 to 5.3)	0.0051	2.1 (1.3 to 7.5)	0.010
Fontan age (+1 SD)	1.1 (0.8 to 1.4)	0.68		
Male versus female	1.2 (0.6 to 2.3)	0.59		

MIX, mixed or indeterminate ventricular morphology; SLV, single left ventricular morphology; SRV, single right ventricular morphology.

operated with atrial switch when compared with patients with systemic LVs.²⁰ RV morphology in paediatric Fontan patients was associated with worse ventricular and valvar function compared with LV or MIX.²¹ Inadequate ventricular preload may be a major determinant of reduced diastolic function in Fontan patients,^{16 22} although it is not clear whether this affects SLV and SRV in the same manner. In summary, pathophysiological data suggest that the performance of hearts with SRVs—including SRVs in Fontan patients, is inferior to the function of hearts with SLV. These data are in agreement with observations that patients with SRVs have a high frequency of heart failure and high mortality.^{23 24}

Similarly, our study demonstrated a significantly better survival in patients with SLV compared with patients with SRV, mainly associated with differences in incidence of death or HTX due to heart failure. This finding was in fact predicted by an Editorial in 2008,¹ based on a retrospective study of 261 Fontan patients from Boston operated in 1973–1991 suggesting increased long-term mortality due to heart failure in patients with SRV.⁷ The present study is the first to confirm this hypothesis. Moreover, our findings do not only apply to excess mortality due to heart failure in patients with SRV with Fontan circulation, but throughout the surgical treatment process of patients with UVH.

According to our data, patients with SLV had favourable survival when compared with patients with SRV both with and without HLHS, and these differences were seen both in Fontan and non-Fontan patients. One of the studies from Australia and New Zealand reported that HLHS was a predictor of adverse events in Fontan patients, whereas data specifically focusing on non-HLHS SRV were not provided.⁹ Our data indicate that the negative prognostic impact of right ventricular morphology is not limited to HLHS, but encompasses a broader spectrum of UVH defects characterised by right ventricular morphology—a suggestion further supported by the observation that survival in SRV diagnostic subgroups was poorer than SLV survival, and that survival in SLV diagnostic subgroups was better than SRV survival (online supplementary figure 1).

Limitations

Distinguishing between right versus left ventricular morphology in patients with UVH may be difficult.

Although we have tried to adhere to an established classification scheme,¹² determination of definite ventricular morphology is sometimes impossible. Therefore, we defined a group denoted ‘mixed or indeterminate morphology’.

In later surgical eras, there was a marked sequential improvement in survival in patients undergoing Fontan surgery. However, after exclusion of early deaths, the differences between eras were much smaller. Given the shorter follow-up duration of patients with extracardiac Fontan compared with patients with lateral tunnel Fontan, we were unable to determine whether this impacts survival. There was a sequential increase in the number of patients with UVH having Fontan surgery despite stable birth incidence—suggesting that more patients previously considered inoperable are now operated. The number of Fontan patients doubled from 1991–2000 to 2011–2015, likely as a result of the shift in surgical technique from direct Fontan to a staged procedure,^{25 26} making more patients suitable for Fontan surgery.

Echocardiographic and haemodynamic studies were done several times prior to all surgical procedures in all of our patients, but standardised data were not available for the present study. Such data might have allowed for a deeper understanding of the significance of SRV versus SLV in relation to survival. As mentioned above, it has, for example, been hypothesised that low ventricular preload may be an important determinant of diastolic function in Fontan patients.^{16 22} Echocardiographic and invasive data might have helped to elucidate the role of diastolic dysfunction as a cause of poor outcome due to heart failure in our patients. Factors like low birth weight, prematurity and genetic syndromes clearly affect survival, and availability of such data might have been valuable. Further studies are needed to explore these important issues.

CONCLUSIONS

Our prospective, long-term follow-up study with low selection bias shows that SRV is a strong predictor of death or HTX in patients with UVH both prior to and following Fontan surgery. This increased risk among patients with SRV compared with patients with SLV may be driven mainly by differences in risk of death or HTX

due to heart failure. Importantly, the increased risk is not confined to patients with SRV with HLHS, but includes a broader group of patients with UVH with RV morphology.

According to our data, ventricular morphology should be included as an important risk factor in the initial evaluation for surgical treatment of patients with UVH. After establishment of Fontan circulation, there should be particular emphasis in patients with SRV on early treatment of potentially modifiable risk factors for development of heart failure, like volume or pressure overload. Finally, there is a need for more studies to define subgroups of patients with SRV who are at particularly high risk.

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Contributors GE wrote the manuscript with input from all authors. JA, JL and HLL participated in conceiving the project and revised it critically for intellectual content. KL was the main responsible for the statistical analyses. GD, GE and HLL participated in data acquisition. MEE, OG and HS revised the paper critically for intellectual content. All authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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