Predicting outcome after Fontan palliation: a single-centre experience, using simple clinical variables

Katrien DE VADDER[1], MD; Alexander VAN DE BRUAENE[1], MD; Marc GEWILLIG[1], MD, PhD; Bart MEYNS[2], MD, PhD; Els TROOST[1], MD; Werner BUDTS[1], MD, PhD

[1]Pediatric and congenital cardiology, University Hospitals Leuven, Leuven, Belgium, [2]Congenital cardiac surgery, University Hospitals Leuven, Leuven, Belgium.

Background The Fontan procedure has become the procedure of choice for patients with one functional ventricle. Although perioperative mortality has decreased, late failure of the Fontan circulation remains a major concern. We aimed at (i) describing Fontan patient characteristics and (ii) identifying simple risk factors for outcome.

Methods Seventy-three patients (median age 23 y (IQR 19-29 y), 60.3% male) were selected from the database of congenital heart defects. Follow-up data were collected. The primary end point was composed by death, resuscitation, or heart transplantation.

Results The most frequently occurring defect was tricuspid atresia (41.1%). Twenty-five (34.2%) and 48 (65.8%) patients received an intra- and extracardiac conduit, respectively. Ten patients reached the primary end point (13.7%) after a median follow-up time of 16 years (IQR 14-19 y). NYHA classification (OR 63.0; 95% CI 6.7-592.4; $P \leq 0.001$), atrioventricular-valve regurgitation (OR 10.6; 95% CI: 1.2-94.1; $P = 0.034$), ventricular function (OR 4.8; 95% CI 1.7-13.7; $P = 0.003$), oxygen saturation (OR 0.7; 95% CI 0.1-1.0; $P = 0.002$) and the presence (OR 8.6; 95% CI 1.6-45.2; $P = 0.011$) or history of supraventricular arrhythmia (OR 6.7; 95% CI: 1.3-35.0; $P = 0.025$), all parameters gathered at the latest follow-up, were associated with outcome. An association was also found with the presence of an intracardiac conduit (OR 5.8; 95% CI 1.4-25.1; $P = 0.018$), higher age at Fontan procedure (OR 1.2; 95% CI 1.0-1.3; $P = 0.007$) and male gender (OR 0.2; 95% CI 0.1-1.0; $P = 0.047$).

Conclusions Complications were not uncommon later after Fontan surgery. Several demographic and procedure-related data were associated with adverse outcome. Interestingly, the strongest correlation was found with clinical and basic echocardiographic characteristics at the latest follow-up.

Keywords *Fontan – outcome – echocardiography.*

INTRODUCTION

In normal biventricular hearts the pulmonary and systemic circulations are in series and are each driven by a ventricle. In patients with a univentricular heart both circulations are in parallel and saturated and desaturated blood is mixed. The Fontan operation separates the pulmonary and systemic circulation and places them in series, both then only supported by one single ventricular chamber[1-3].

The Fontan operation, first reported in 1971 in patients with tricuspid atresia, is now used in a wide range of congenital heart defects, irrespective of the morphology of the dominant ventricle. It has now become one of the most used operations for complex congenital heart defects[2,4].

The technique itself has undergone many modifications. By the late 1980s the classic atriopulmonary connection (RAPA) was replaced by a new concept of total cavopulmonary connection (TCPC): initially with an intracardiac (lateral tunnel) and later with an extracardiac conduit[3,5].

Due to these technical improvements, along with advances in peri-operative care, improvements in anaesthesia management and better patient selection, early mortality has decreased to levels below 5% [6-8] and 15-year

Address for correspondence:

Werner Budts MD, PhD, Congenital Cardiology, University Hospitals Leuven, Herestraat 49,
B-3000 Leuven, Belgium.
E-mail: werner.budts@uzleuven.be

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survival rate increased from 73% in 1990[9] to 81% in 2007[10] and 81.6% in 2011[11].

Although the early and mid-term results of the Fontan state are excellent, late attrition of the Fontan circulation is still a major concern. Patients are prone to develop arrhythmias, heart failure and progressive rise in pulmonary vascular resistance[9,10].

Literature has extensively addressed the outcome of multiple Fontan series and tried to identify potential risk factors, such as the surgical technique used and perioperative parameters (underlying diagnosis, intra- versus extracardiac Fontan)[10,12]. Few data, however, address the role of simple clinical variables during follow-up in predicting adverse outcome. Therefore, our aim was (i) to describe the Fontan population at adolescent and adult age in our institution and (ii) to identify clinical variables related with serious adverse outcome.

SUBJECTS AND METHODS

Study population

We retrospectively reviewed the medical records of all consecutive patients with congenital heart defects who underwent Fontan palliation in a tertiary care hospital (University Hospitals Leuven, Leuven, Belgium), older than 16 years at inclusion and operated after 1982. Patient data were extracted from medical records. This observational retrospective protocol was reviewed and approved by the hospital's Institutional Review Board, all data were anonymously processed, and the ethics committee waived informed consent.

Data collection and definitions

All patients were followed at least once yearly in the outpatient clinic of adult congenital heart diseases. A follow-up visit consisted of a careful history, a detailed physical examination, an electrocardiogram, a standardized echocardiography, and additional tests if indicated. Demographic data (age, gender) and procedure-related data (underlying medical condition, type of surgery, age at Fontan operation) were collected retrospectively. The medical history was thoroughly reviewed to identify complications during follow-up (i.e. thrombo-embolic complications (TEC), arrhythmia, need for catheter-ablation or pacemaker implantation, the occurrence of protein-losing enteropathy). Rhythm data were obtained by analysis of the electrocardiograms and Holter examinations, if available. Arrhythmia was defined as any rhythm different from sinus rhythm, but unifocal extrasystoles were not considered pathologic. A serious adverse event (SAE) was defined as death, cardiac resuscitation or heart transplantation.

At the last available or the latest visit before a SAE clinical parameters (NYHA class, body weight, length, blood pressure, transcutaneous oxygen saturation at rest) and technical data (ventricular function, atrioventricular valve regurgitation (AVVR)) were collected. Ventricular function and AVVR were evaluated by transthoracic echocardiography. AVVR was graded on a scale from 0 to 4 and moderate regurgitation was defined as at least 2/4. Ventricular function was assessed with the M-mode or Simpson method, where applicable (depending on the quality of the acoustic window). Normal ventricular function was defined as an ejection fraction $\geq 55\%$, mildly impaired between 45 and 55%, moderately impaired between 35 and 45%, seriously impaired $< 35\%$. When available, the most recent data from a right heart catheterization were collected. Finally, biochemistry results and medication were also noted.

Statistical analysis

Data are reported as percentage for categorical variables and as mean ± SD or median with interquartile range (IQR, 25-75%), as appropriate, for continuous variables. Logistic regression analysis with serious adverse event as dependent variable and clinical and technical parameters as independent variables was performed. ROC analysis was done for transcutaneous oxygen saturation at rest. Kaplan Meier curves were plotted to depict event-free survival. Kaplan Meier curves were compared using log rank test. All tests of significance were two-tailed and a *P*-value of < 0.05 was considered significant. Results were analysed with SPSS 20 (SPSS Inc., Chicago, USA).

RESULTS

Patient characteristics and clinical data

The study cohort comprised 73 consecutive Fontan patients. Median follow-up time was 16 y (IQR 14-19 y). Of the patients enrolled, 60.3% were male and the median age was 23 y (IQR 19-29 y). Most frequent underlying pre-operative diagnosis was tricuspid atresia (41.1%). At the latest follow-up, most patients functioned in NYHA class I or II (80.6%). Mean blood pressure was within the normal range and the mean transcutaneous oxygen saturation at rest was 93 ± 5%. Several patients were treated with a beta blocker (22.5%). More than half of the patients (51.4%) received acetylsalicylic acid (ASA). Other details are summarized in table 1.

Procedure-related characteristics

Fifty-nine patients underwent maximum two palliative procedures before the first Fontan completion. An

overview of these preceding interventions is given in figure 1. The first Fontan operation was performed at a median age of 5 years (IQR 3-9 y). This *first step* in Fontan completion consisted of a RAPA in 30 patients (41.1%), a lateral tunnel in 6 patients (8.2%) and an extracardiac conduit in 21 patients (28.8%). Other procedures included a Kawashima operation, a classic Glenn shunt, a bidirectional cavapulmonary anastomosis, a hemi-Fontan and an atrioventricular connection (RA-RV) in 1 (1.4%), 1 (1.4%), 6 (8.2%), 4 (5.5%) and 4 patients (5.5%), respectively. After a median follow-up time of 8 y (IQR 6-11 y), 29 patients (39.7%) underwent a *second step* Fontan procedure. In most patients (26/29; 90%) this consisted of a conversion to an extracardiac conduit. One patient received a RAPA (3.5%), 1 patient was converted to a lateral tunnel (3.5%) and 1 patient underwent AV valve surgery (3.5%). Only 2 patients (2.7%) underwent a *third step* re-intervention, 1 month and 7 years later, respectively. One patient had AV valve surgery and the other received an extracardiac conduit. No patients died between interventions. In total, a vast majority (65.8%) received an extracardiac conduit. The final distribution of the type of Fontan procedure is shown in table 2.

Echocardiographic, biochemical, and catheterization data

At last available or latest follow-up before a SAE the majority of Fontan patients still show a preserved or mildly impaired systolic ventricular function (90%), as shown in table 3. Moderate AV valve regurgitation was present in 41% of patients. Biochemical data are also listed in table 3. Catheterization data were available for 60 patients (82%). Mean central venous pressure (CVP) was 12 ± 4 mmHg.

Complications and serious adverse events during follow-up

Arrhythmias were most frequently seen and in all cases this consisted of supraventricular arrhythmias. Eighteen patients showed a trombo-embolic complication (24.6%). In 8.2% a thrombus in the Fontan circulation was noticed. Only two cases of protein-losing enteropathy (PLE) were identified. SAEs were noted in ten patients at a median follow-up time of 10 months (IQR 3-16) since latest visit to the outpatient clinic (except for the patient who was resuscitated). The distribution of all complications is summarized in table 4. Figure 2 and 3 show a Kaplan-Meier curve of the event-free survival of our total study population (absence of serious adverse events) and after correction for the final type of Fontan procedure.

Table 1 Patient's history, physical examination, and treatment

Age (y, median), (IQR 1-3)	23 (19-29)
Gender (male, n, %)	44/73 (60.3)
Underlying diagnosis (n, %)	
1. Tricuspid valve atresia	30/73 (41.1)
2. Pulmonary atresia with intact ventricular septum	7/73 (9.6)
3. Double-inlet left ventricle	19/73 (26)
4. Hypertrophic left heart syndrome	1/73 (1.4)
5. Unbalanced (atrio)ventricular septal defect	9/73 (12.3)
6. Other	7/73 (9.6)
NYHA (x/IV, n, %)	
I	19/72 (26.4)
II	39/72 (54.2)
III	13/72 (18.1)
IV	1/72 (1.4)
Length (m, mean ± SD)	1.67 ± 0.9
Weight (kg, mean ± SD)	61 ± 14
Systolic BP (mmHg, mean ± SD)	115 ± 18
Diastolic BP (mmHg, mean ± SD)	71 ± 12
SaO2 (%, mean ± SD)	93 ± 5
Medication (n, %)	
ACE-inhibition	24/71 (33.8)
Beta blocker	16/71 (22.5)
Diuretics	16/72 (21.9)
Amiodarone	5/68 (7.4)
Digoxin	14/68 (20.6)
Antiplatelet or anticoagulation (n, %)	
1. No	7/72 (9.7)
2. ASA	37/72 (51.4)
3. Acenocoumarol	25/72 (34.7)
4. ASA + clopidogrel	3/72 (4.2)

ACE: angiotensin-converting enzyme, ASA: acetylsalicylic acid, SaO2: transcutaneous oxygen saturation, BP: blood pressure.

Table 2 Final distribution of procedures (n, (%))

RAPA	16/73 (21.9)
Lateral tunnel	7/73 (9.6)
Extracardiac conduit	48/73 (65.8)
RA-RV	2/73 (2.7)

RAPA: atriopulmonary connection; RA-RV: atrioventricular connection.

Table 3 Echocardiographic, biochemical, and catheterization data at last follow-up

Systolic ventricular function (n, %)	
Preserved	40/70 (57.1)
Mildly impaired	23/70 (32.9)
Moderately impaired	6/70 (8.6)
Seriously impaired	1/70 (1.4)
Moderate AVVR (≥ 2/4) (n, %)	28/68 (41.2)
Biochemical results	
Haemoglobin (g/dl, mean, ± SD)	15 (14-16)
Haematocrit (%, mean, ± SD)	44 (41-49)
Creatinin (mg/dl, median, IQR 1-3)	0.89 (0.75-1.01)
CVP (mmHg, mean ± SD)	12 ± 4

AVVR: atrioventricular valve regurgitation; CVP: central venous pressure.

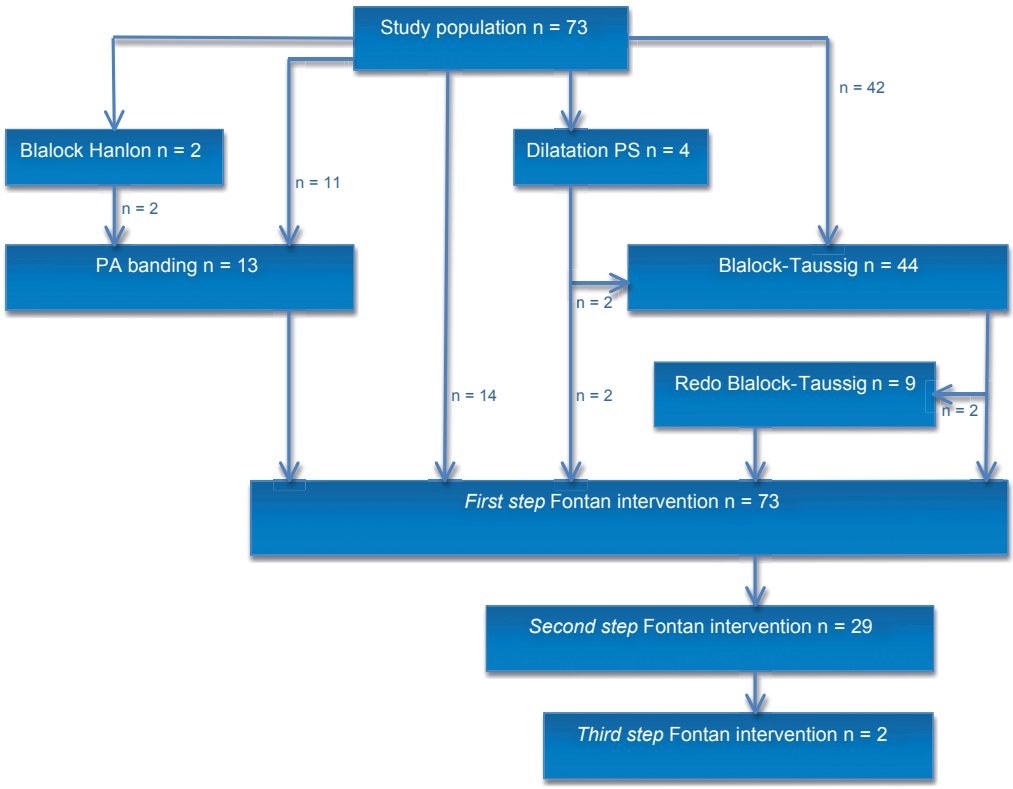

Fig. 1 Flow chart of procedural steps to end with the final type of Fontan circulation.

Table 4 Complications and serious adverse events during follow-up

Thromboembolic complications (n, %)	
No	55/73 (75.3)
Pulmonary embolism	3/73 (4.1)
Thrombus in Fontan circulation	6/73 (8.2)
Stroke	3/73 (4.1)
DVT extremity	4/73 (5.5)
Other	2/73 (2.7)
Arrhythmia (n, %)	
Before completion of extracardiac conduit	28/70 (40)
After completion of extracardiac conduit	25/71 (35.2)
Pacemaker (n, %)	14/73 (19.2)
Attempts for ablation (n, %)	
0	59/73 (80.8)
1	5/73 (6.8)
2	8/73 (11)
4	1/73 (1.4)
Protein-losing enteropathy (n, %)	2/73 (2.7%)
Major adverse cardiac event (n, %)	
No	63/73 (86.3)
Resuscitation	1/73 (1.4)
Heart transplantation	3/73 (4.1)
Death	6/73 (8.2)

DVT: deep venous thrombosis; TCPC: total cavo-pulmonary connection.

Risk factors for serious adverse events

Univariate analysis showed a correlation between both predetermined and clinical variables and the occurrence of a SAE. The strongest correlation was found with functional class (NYHA), ventricular function and AVVR, both obtained by echocardiography, and the transcutaneous oxygen saturation (SaO2). ROC analysis was done on this last variable and showed that a SaO2 of ≤ 86% has a sensitivity of 95% and a specificity of 83% to be related with SAE. The complete list of factors associated with adverse outcome is outlined in table 5.

DISCUSSION

This retrospective study was set up to describe the population that underwent a Fontan operation at our institution since 1982 and to identify simple risk factors for serious adverse outcome.

The patient population in our centre is predominantly young and belongs mostly to NYHA class I to II. The majority of patients first underwent palliative intervention at a very young age. In most cases this consisted of a Blalock-Taussig shunt. Median age at first Fontan completion was 5 years. The type of Fontan surgery varied. In the early part of our experience we applied the RAPA connection and later on a (intracardial) lateral tunnel was

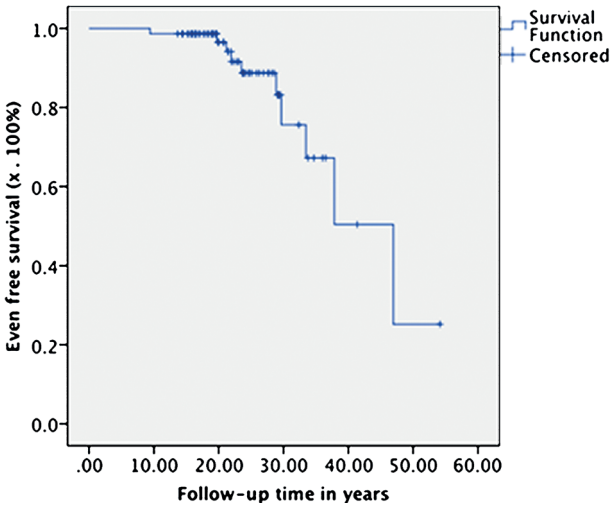

Fig. 2 Kaplan-Meier survival curve for serious event-free survival.

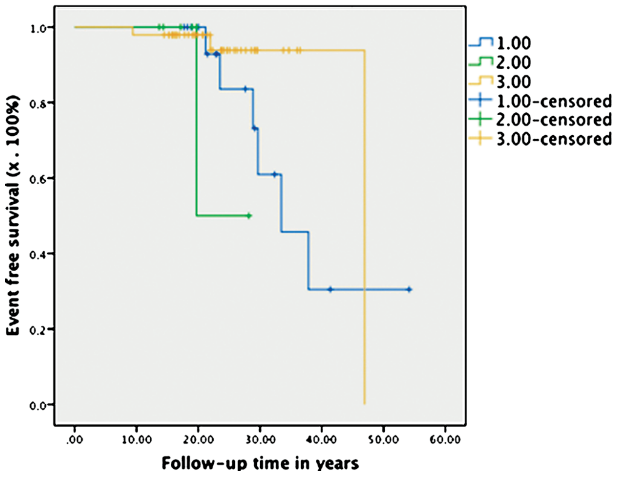

Fig. 3 Kaplan-Meier survival curve for serious event-free survival per type of final Fontan circulation; log rank test p = 0.1; (1) lateral tunnel, (2) other atrio-pulmonary connection, atrio-ventricular connection, (3) extracardiac conduit.

Table 5 Risk factors associated with serious adverse events

Risk factor	OR (95% confidence interval)	*P*-value
Male gender (y/n)	0.230 (0.054-0.979)	0.047
Age at Fontan operation (years)	1.164 (1.043-1.299)	0.007
Intracardiac conduit (y/n)	5.833 (1.356-25.088)	0.018
History of arrhythmia (y/n)	6.667 (1.270-34.987)	0.025
Presence of arrhythmia (y/n)	8.556 (1.620-45.195)	0.011
NYHA (I, II, II, IV)	62.969 (6.693-592.378)	< 0.001
SaO2 (%)	0.688 (0.543-0.871)	0.002
Ventricular function (preserved > seriously impaired)	4.836 (1.711-13.669)	0.003
AVVR (≥2/4)	10.636 (1.202-94.145)	0.034

y/n: yes or no; SaO2: transcutaneous oxygen saturation; AVVR: atrioventricular valve regurgitation.

constructed. However, 65.8% of our patients finally received an extracardiac conduit. Our figures corresponded very well to those given in the literature[10,13-16].

During follow-up of our population we noted multiple adverse events ranging from exclusively supraventricular arrhythmias, development of heart failure, thrombo-embolic complications to protein-losing enteropathy. These complications are well described in the literature and define the significant morbidity still seen in early survivors of the Fontan operation[3,13,17-19].

The primary end point, defined as sudden cardiac death, heart transplantation or the need for resuscitation was reached in 13.7% of patients. Univariate statistical regression analysis was performed; some factors were identified to be associated with serious adverse outcome. Some were indeed predetermined such as male gender or older age at Fontan surgery. However, six of the identified variables were clinical data collected at the time of the last outpatient visit (maximally 1 year before the serious adverse event).

Higher age at surgery was already considered as a risk factor when Seliem et al. showed that a larger amount of left ventricular hypertrophy was associated with less satisfactory clinical results. The precise mechanism responsible for ventricular hypertrophy and impaired left ventricular function remains unclear, but long-standing volume overload and hypoxaemia (and higher age at surgery) are possibly the main factors involved[20]. A recent study from Rogers et al.[12]reviewed peri-operative outcomes of cohorts of patients of different eras, due to shift in clinical practice. A trend existed towards performing Fontan completion at an older age, presumably to place a sufficiently large extracardiac conduit. The group undergoing Fontan completion at older age

showed more than mild atrio-ventricular valve regurgitation, higher end-diastolic ventricular pressures and more frequently needed additional procedures at the time of the Fontan operation, suggesting it was a higher risk cohort[12]. Some evidence exists that older age at Fontan completion is associated with a higher incidence of arrhythmias, while this association is not seen with other complications such as thrombo-embolism or protein-losing enteropathy[21,22].

Also the *type of surgery* seems to be a well-established factor associated with outcome. In 2007 d'Udekem et al. showed that patients with RAPA connections were more likely to experience arrhythmias and symptoms of heart failure with a significant difference in 15-year survival[10]. Other data confirm this finding[10,13,14,23,24]. New surgical techniques appeared such as the lateral tunnel and the extracardiac conduit. There is no agreement, however, regarding the superiority of one type of modification over the other in terms of long-term outcome. A recent study suggests superior results on early outcome with a lateral tunnel Fontan compared to extracardiac conduit[5]. In our population we found all intracardiac Fontans (RA-AP and lateral tunnel) to be related with adverse outcome, but difference in outcome between lateral tunnel and extracardiac conduit was not studied because of lack of power.

The presence or a history of *supraventricular arrhythmias* was also significantly associated with adverse outcome. The strongest correlation was found with the presence of arrhythmia at the time of consultation. Arrhythmia is a well-known complication causing morbidity and mortality in the surviving Fontan population and is said to have the greatest impact on daily functioning[5,14]. Alphonso et al. found in 2005 that arrhythmias at any time post-operatively were significantly associated with a poorer outcome[5,13].

We found more arrhythmias before completion of an extracardiac conduit. It is clear from observational studies that RAPA connections are more prone to arrhythmic events[25-27]. In this group of patients arrhythmia in itself can be a reason for Fontan conversion since ablation in large atrial structures is often ineffective.

However, the strongest association was found with simple *anamnestic, clinical and echocardiographic features*: NYHA classification, atrio-ventricular valve regurgitation, ventricular function, and oxygen saturation at rest. Of these features NYHA showed the strongest correlation. A higher NYHA classification gives a 62-times higher chance to present with a serious adverse event within one year. An oxygen saturation of ≤ 86% has a sensitivity of 95% and a specificity of 83% to be related with adverse outcome.

Multivariate analysis was not performed because of the small study population and we hypothesize that these risk factors probably all point out the same problem: a worsening haemodynamic situation. An important finding, however, is that functional class seems a stronger predictor of outcome than the objective values of valve insufficiency or ventricular function.

Some recent studies also examined the value of clinical features in predicting worse outcome. In 2008 Khairy et al. reported diuretic therapy as an independent risk factor for mortality or transplantation[15]. In 2010 Diller et al. published a retrospective study of 321 patients where the role of cardiopulmonary exercise testing and other (clinical) variables was studied in predicting adverse outcome at mid-term follow-up[14]. Besides clinically relevant arrhythmias, symptoms of heart failure requiring diuretic therapy were found to be strongly associated with poor outcome. Unlike Diller et al. we found simple echocardiographical parameters to also correlate with serious adverse events. This is relevant since many Fontan patients are not able to perform exercise testing and physicians are often obliged to rely on simple clinical tests and basic examinations. Another important difference in our study is the clear time interval between the appearance of symptoms and the adverse event that results from the set-up of the study. To our knowledge this is the first study in Fontan patients where echocardiographic data at routine follow-up are shown to be useful in predicting outcome within the coming year. Our findings thus support a follow-up strategy using a detailed history, a good physical examination and a standardized echocardiography to select those patients at risk of a major adverse event in the next year. This offers a simple way to define a 'high-risk group', requiring more intensive follow-up.

Besides modality of follow-up and definition of high-risk groups within the Fontan population, an important topic in the future treatment of Fontan patients will be how to approach the major problem of arrhythmias. Already extensively described in the literature, we also found arrhythmias to be a frequent complication during follow-up, especially in the older Fontan patient with a RAPA connection. Should we be more aggressive in converting well-functioning RAPA connections to prevent arrhythmic problems? This question is subject to further investigation.

Our study has several limitations. First, it was a single-centre study resulting in a rather small study population. That may explain why some risk factors described in the literature were not found to be relevant in our study population (underlying diagnosis, presence of abnormal pulmonary venous drainage, morphology of the single ventricle, PLE, heterotaxia syndrome)[11,15,28]. Secondly, the small number of serious adverse events did not allow us to perform a multivariate analysis to detect independent predictors of adverse outcome. Thirdly, the estimation of the ventricular function with echocardiography had

certain methodological disadvantages relative to other imaging modalities such as magnetic resonance imaging. Fourthly, pulmonary vasculare resistance was not routinely measured during follow-up. This can cause a bias because an increasing resistance is a well-known factor in failing Fontan and can be related to a decline in functional class. Also the difference in outcome between a lateral tunnel and extracardiac conduit was not compared because of lack of power.

CONCLUSION

The aim of this study was to describe the Fontan population in our centre and to identify risk factors associated with adverse outcome within the next year.

The Fontan operation has come a long way from being purely palliative with a very short life expectancy to a complex (staged) surgical technique, which has prolonged life expectancy of the population as well as the quality of life. Still, a significant number of adverse events cause important morbidity and mortality.

In our mostly male and young Fontan population we state that simple clinical and echocardiographic features may predict a serious adverse event within the next year. Of these features NYHA classification is the most important one. Although a subjective parameter, we could show that in measuring SaO2, LV function and AVVR, one can identify a group of high-risk patients.

Specialized patient care in a tertiary centre is required to track these patients at higher risk and offer them closer follow-up.

CONFLICT OF INTEREST: none.

LIST OF ABBREVIATIONS

AVVR: atrioventricular valve regurgitation
CI: confidence interval
CVP: central venous pressure
IQR: interquartile range
NYHA: New York Heart Association
OR: odds ratio
RAPA: atriopulmonary connection
SAE: serious adverse event
TCPC: total cavopulmonary connection
TEC: thrombo-embolic complications

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