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Predictors of morbidity and mortality in contemporary Fontan patients: results from a multicenter study including cardiopulmonary exercise testing in 321 patients

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Aims Previous studies have established an association between exercise intolerance and increased morbidity and mortality in congenital heart disease patients. We aimed to clarify if exercise intolerance is associated with poor outcome in Fontan patients and to identify risk factors for mortality, transplantation, and cardiac-related hospitalization.

Methods and results A total of 321 Fontan patients (57% male, mean age 20.9 ± 8.6 years) who underwent cardiopulmonary exercise testing (CPET) at four major European centres between 1997 and 2008 were included. During a median follow-up of 21 months, 22 patients died and 6 patients underwent cardiac transplantation (8.7%), resulting in an estimated 5-year transplant-free survival of 86%. Parameters of CPET were strongly related to increased risk of hospitalization, but—with the exception of heart rate reserve—unrelated to risk of death or transplantation. In contrast, patients with clinically relevant arrhythmia had a 6.0-fold increased risk of death or transplantation ($P < 0.001$). Furthermore, patients with atriopulmonary/-ventricular Fontan had a 3.7-fold increased risk of death or transplantation compared with total cavopulmonary connection patients ($P = 0.009$). The combination of clinically relevant arrhythmia, atriopulmonary/-ventricular Fontan, and signs of symptomatic or decompensated heart failure was associated with a particularly poor outcome (3-year mortality 25%).

Conclusion On short-term follow-up, most parameters of CPET are associated with increased risk of hospitalization but not death or transplantation in contemporary Fontan patients. Only decreased heart rate reserve and a history of clinically relevant arrhythmia, atriopulmonary/-ventricular Fontan, and/or heart failure requiring diuretic therapy are associated with poor prognosis, potentially identifying patients requiring medical and/or surgical attention.

Keywords Adult congenital heart disease • Exercise testing • Prognosis • Fontan operation

Introduction

Previous studies have suggested that exercise intolerance is a powerful prognostic marker in patients with congenital heart disease.[1–3] More recently, studies have shown the prognostic value of parameters of cardiopulmonary testing in patients with a systemic right ventricle or corrected Tetralogy of Fallot.[4,5] As a consequence, a peak oxygen uptake (peak VO_2) <15 mL/kg/min

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or <50% of predicted for age and sex has been recommended for consideration of congenital heart disease patients for cardiac transplantation according to current ACC/AHA guidelines (Class IIa, Level of Evidence: C).[6]

Patients with Fontan physiology are affected by a multitude of complications associated with considerable morbidity and mortality, and are frequently considered possible candidates for cardiac transplantation.[7–11] However, due to limited numbers of Fontan patients included in previous studies the prognostic value of cardiopulmonary testing in these patients is unknown.

This retrospective study included all Fontan patients who underwent cardiopulmonary exercise testing (CPET) with gas exchange monitoring at four major European centres for congenital heart disease between 1997 and 2008. All centres have long-standing experience with CPET in patients with congenital heart disease and have collaborated on cardiopulmonary exercise studies previously.[4,5,12]

In addition to parameters of exercise testing, the prognostic value of simple baseline clinical information such as the morphology of the single ventricle, symptoms, functional class, type of surgery, the presence of clinically relevant arrhythmias, and signs and symptoms of heart failure were considered.

Methods

This was a multicentre retrospective investigation. Across the four institutions involved, all Fontan patients who are able to exercise undergo routine CPET as part of their regular clinical follow-up. All Fontan patients who underwent a cardiopulmonary exercise test between April 1997 and December 2008 were included. In patients who underwent more than one test during the study period, only the first test was considered. Patients with a partial cavopulmonary anastomosis (i.e. Glenn-type palliation) were excluded from the present study. Based on the type of Fontan operation, patients were classified as atriopulmonary Fontan, atrioventricular Fontan, lateral tunnel total cavopulmonary anastomosis, or extracardiac conduit total cavopulmonary connection (TCPC). In addition to parameters of CPET, the following variables potentially associated with outcome were studied: a history of clinically relevant (usually supraventricular) arrhythmia, history of decompensated heart failure requiring diuretic therapy, morphology of the functional single ventricle, and previous palliations. Clinically relevant arrhythmia was defined based on symptoms, documentation, and need for chronic antiarrhythmic medication.[13] Informed consent was obtained from all patients before undergoing exercise testing. The institutional committees on human research approved the present retrospective study.

Follow-up and analysis of survival status and hospitalization

The primary endpoint of the study was a combined endpoint of death or cardiac transplantation. To assess morbidity, we also investigated an endpoint of cardiac-related hospital admissions. Cardiac-related hospital admissions were defined as any admission directly caused by heart failure requiring inpatient care or arrhythmia requiring hospital treatment. In addition, complications characteristic of the Fontan circulation such as protein losing enteropathy were classified as cardiac-related hospitalizations for the scope of the study. Following the exercise test, all patients were regularly followed up for cardiac-related events at their respective institutions, providing for a high likelihood that all cardiac events would have been recorded. Additionally, patients' medical records were reviewed to obtain information on reasons for hospitalization and patients' survival status. Survival status was further ascertained from phone interviews with patients' primary care physicians. No patient was lost to follow-up during the follow-up period.

Cardiopulmonary exercise test

Exercise tests were performed on an electronically braked ergometer cycle ($n = 236$) or on a treadmill ($n = 85$). Carbon dioxide elimination, VO_2, and minute ventilation were measured with a computerized breath-by-breath analyser. Patients performed a symptom-limited maximal exercise test using an incremental protocol that allowed reaching exhaustion in ~10 min of exercise. A 12-lead electrocardiogram and transcutaneous oxygen saturation were also continuously monitored throughout the study, and blood pressure was determined manually every 2 min. The technical details of measurement of peak VO_2 and VE/VCO_2-slope have been published.[1,3,12] Resting heart rate was measured after at least 2 min of complete rest in a seated position, whereas peak heart rate was defined as the maximal heart rate achieved during exercise. Heart rate reserve was calculated as the difference between peak and resting heart rates.[2] Standard equations were used to generate predicted values for peak exercise parameters.[14] Because of age-related differences of normal peak VO_2 when expressed in mL/kg/min, peak VO_2 was also expressed as % of predicted value.[15] Anaerobic threshold was determined according to Beaver *et al.*[16]

Statistical analysis

Values are presented as mean ± standard deviation (SD) or median and inter-quartile range (IQR; 25th and 75th percentile). Categorical variables are presented as frequencies and percentages. Comparisons between subgroups were performed by unpaired *t*-test. Possible correlations between demographic, clinical, and exercise variables and outcome were investigated using univariate Cox proportional-hazard analyses. The hazard ratio with two-sided 95% confidence intervals is provided. Given the limited number of endpoints, we chose not to perform multivariate analyses. Instead, where appropriate, bivariate analyses were performed. Time-dependent receiver operating characteristic (ROC) curves from censored survival data using the Kaplan–Meier method of Heagerty, Lumley, and Pepe[17] were employed to further investigate the prognostic value of exercise parameters. In addition, different cut-off values were examined by maximizing the log-rank χ^2 statistic.[18] The comparative importance and additional value of the clinical score and parameters of cardiopulmonary exercise test were also assessed with a random survival forest method using the prediction error, which is conceptually similar to the area under the receiver curve as described in detail previously.[19,20] In addition, rank-hazard plots were constructed to visualize the relative importance of covariates in a proportional hazards model.[21] Covariate values are ranked and the relative hazard is plotted as a function of ranks scaled to interval. This transformation allows comparing the prognostic relevance of covariates measured in different units. Statistical analysis was performed with R version 2.4.1[22] and MedCalc 10.1.2.0 (MedCalc Software, Mariakerke, Belgium). For all analyses, a two-tailed probability value <0.05 was used as the criterion for statistical significance.

Results

Patient characteristics

The study cohort consisted of 321 patients (152 from the German Heart Centre Munich, 85 from the Royal Brompton Hospital London, 54 from the University Hospital Bologna, and 30 from

the Great Ormond Street Hospital London) with a mean age of 21 ± 9 years. *Table 1* summarizes baseline characteristics in all patients based on type of Fontan surgery. The type of Fontan operation was an atriopulmonary Fontan in 35%, an atrioventricular Fontan in 12%, a lateral tunnel total TCPC in 30%, and an extracardiac conduit TCPC in 23% of patients. Underlying cardiac diagnoses were tricuspid atresia in 52%, double inlet left ventricle in 16%, double outlet right ventricle in 10%, pulmonary atresia with intact ventricular septum in 7%, and other complex conditions in 15%. Overall, 4.4% had atrial isomerism. Thirty-one percentage of patients had undergone previous Glenn-type palliation.

Cardiopulmonary exercise testing

Peak VO_2 was markedly reduced in Fontan patients. Only 2.7% of patients had a borderline (i.e. 80–90% of predicted) and only 1% of patients had a normal peak VO_2 as shown in *Figure 1*. No significant difference in peak VO_2 was found between patients with atriopulmonary/atrioventricular Fontan and those with lateral tunnel or extracardiac conduit TCPC.

Survival and cardiac transplantation

During a median follow-up of 21 months (IQR 14–42 months), 22 patients died (6.9%) and 6 patients (1.9%) underwent cardiac transplantation due to severe heart failure. As illustrated in *Figure 2A*, almost all patients who died or required cardiac transplantation had undergone an atriopulmonary or atrioventricular Fontan, whereas only three patients with TCPC died (1.8%) and two required cardiac transplantation (1.2%, $P < 0.0001$). To investigate the possibility that younger age confounded this association and accounted for a better outcome in the TCPC group, bivariate Cox proportional-hazard analyses were performed. The type of Fontan operation was found to be significantly related to the risk of death or transplantation independent of age [$P = 0.009$, hazard ratio 3.7 (95% CI 1.4–9.6)] in this analysis. The leading mode of death was sudden, presumably arrhythmic in 29% of patients followed by heart failure (28%), and perioperative mortality during conversion to TCPC prompted by late sequaelae of atriopulmonary or atrioventricular Fontan (19%) as illustrated in *Figure 2B*.

Hospitalization for cardiac reasons/ Fontan complications

Overall, 41% of patients were hospitalized for cardiac-related reasons during follow-up. Again, patients with atriopulmonary or atrioventricular Fontan had a significantly higher risk of cardiac-related hospitalization compared with TCPC patients [hazard ratio 1.7 (95% CI 1.17–2.50), $P = 0.004$] as shown in *Figure 2C*.

Table 1 Selected baseline characteristics

Characteristic	All patients ($n = 321$)	APC/AVC Fontan[a] ($n = 150$)	ltTCPC/ecTCPC ($n = 171$)	*P*-value
Age (years)	21 ± 9	26 ± 7	17 ± 7	**<0.0001**
Gender (% male)	56	54	59	0.48
LV morphology (%)	81	92	72	**<0.0001**
Previous PCPC (%)	31	6	54	**<0.0001**
NYHA I/II/III (%)[b]	42/43/15	35/45/20	54/40/6	**0.0496**
Deaths	22	19	3	**0.0004**
Heart transplantation	6	4	2	0.31
Pacemaker (%)	9	7	10	0.84
Age at Fontan completion (years)	7.1 ± 5.9	7.6 ± 5.7	6.8 ± 5.7	0.31
Class I and III[c] AADs (%)	20	35	7	**<0.0001**
Amiodarone (%)	14	23	5	**<0.0001**
Sotalol (%)	5	9	1	**0.002**
Digoxin (%)	8	13	5	**0.02**
ACE-inhibitors (%)	32	31	34	0.53
Heart rate reserve (b.p.m.)	63 ± 25	64 ± 26	63 ± 24	0.74
Peak VO_2 (mL/kg/min)	22.8 ± 7.4	21.7 ± 7.0	23.7 ± 7.5	**0.01**
% age-predicted peak VO_2	51.7 ± 15.4	53.4 ± 16.3	50.1 ± 14.4	0.07
Peak pulse (b.p.m.)	146 ± 28	140 ± 30	152 ± 25	**0.0001**
Resting pulse (b.p.m.)	83 ± 18	76 ± 16	89 ± 17	**0.004**

ACE, angiotensin-converting enzyme; b.p.m., beats per minute; NYHA, New York Heart Association class; PCPC, partial cavopulmonary anastomosis; Peak VO_2, peak oxygen consumption.
[a]Plus-minus values are mean ± standard deviation.
[b]NYHA class was only available for patients under follow-up at the Royal Brompton Hospital, London and the University Hospital Bologna.
[c]Classification of antiarrhythmic drugs according to Vaughan Williams.
P-values (unpaired *t*-test) for comparison between patients with atriopulmonary (APC) or atrioventricular Fontan and patients with lateral tunnel total cavopulmonary anastomosis (ltTCPC) and extracardiac conduit TCPC (ecTCPC). Significant *P*-values are given in bold.

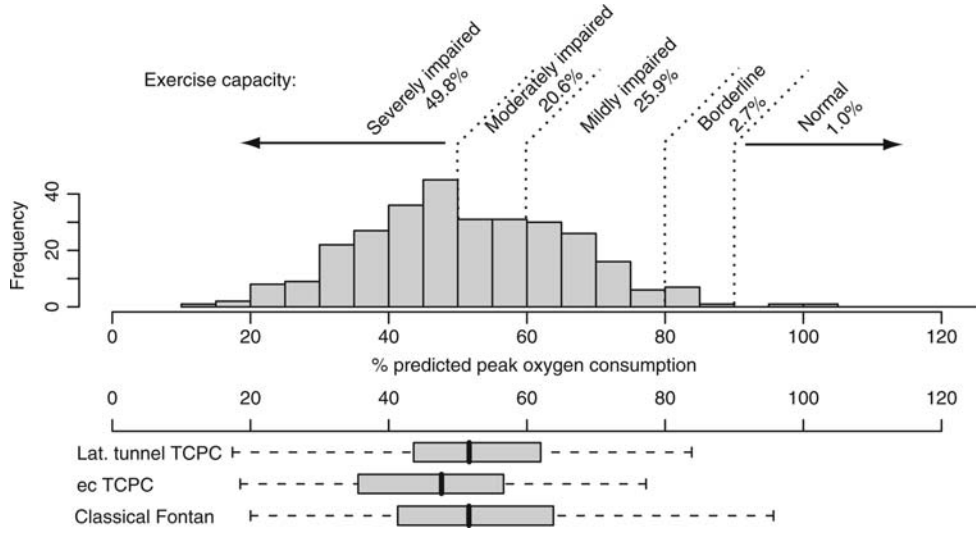

Figure 1 Distribution of % predicted peak oxygen consumption in patients after Fontan operation and its distribution in patients with different types of Fontan surgery.

Prognostic value of parameters of cardiopulmonary exercise testing

All parameters of CPETwere strongly related to cardiac-related hospitalization (*Table 2*). On Cox proportional-hazards analysis, only heart rate reserve was significantly related to survival without cardiac transplantation. The association between heart rate reserve and death or transplantation was independent of the use of antiarrhythmic drugs, patient age, and type of Fontan surgery on Cox proportional-hazards analysis as shown in *Table 3*. A heart rate reserve of 72 b.p.m. was identified by ROC curve analysis as the value corresponding to the highest accuracy for predicting death or need for transplantation (AUC 0.643, $P = 0.0077$). This cut-off value was associated with a sensitivity of 88%; however, the specificity is only 38%. Peak VO_2, percentage predicted peak VO_2, VE/VCO_2-slope, and anaerobic threshold were not related to death or transplantation on time-dependent ROC curve analysis or log-rank χ^2 statistic maximization (data not shown). When considering only patients with a follow-up period above 3 years, no parameter of CPET was significantly related to death or transplantation ($P > 0.05$ for all). To account for the possibility that cyanosis may explain the lack of prognostic information provided by parameters of CPET, we performed subanalyses in patients without cyanosis and without residual right-to-left shunt lesions. However, even after excluding patients with fenestrations and shunt lesions, parameters of CPET (with the exception of heart rate reserve) were not related to outcome. The same results were obtained when patients with resting or exercise saturations <90 or $<85\%$ were excluded.

Prognostic value of medical history and clinical information

In contrast to most parameters of exercise testing, a history of clinically relevant cardiac arrhythmias was found to be strongly related to freedom from death or cardiac transplantation as shown in *Figure 3*. Overall, 33% of patients had a history of clinically relevant arrhythmias [of these 64% were treated with a Class I or III antiarrhythmic drug, 51% with a beta-blocker (not mutually exclusive), and 4% were not medically treated because of contraindications or patient choice]. The majority of patients treated with a Class I or III antiarrhythmic drug received amiodarone (70%), whereas only a minority received sotalol (25%) or Class I drugs (5%). A strong association was also found between clinically relevant arrhythmias and cardiac-related hospitalization, as illustrated in *Figure 3*. In addition, signs and symptoms of heart failure prompting diuretic therapy were strongly related to survival without transplantation or need for hospitalization for cardiac reasons. To exclude the possibility that death associated with conversion to TCPC might account for increased mortality in the atriopulmonary and atrioventricular Fontan cohort and that this may confound the prognostic value of parameters of exercise capacity, the analyses were repeated by censoring patients who underwent TCPC conversion at the time of death. Type of Fontan surgery, clinically relevant arrhythmia, heart failure symptoms requiring diuretic treatment, and heart rate reserve were confirmed as significant prognostic markers for mortality or transplantation in this analysis, whereas peak VO_2, VE/VCO_2-slope, and anaerobic threshold were not related to outcome.

As a non-TCPC type of Fontan operation, a history of clinically relevant arrhythmia and signs and symptoms of heart failure prompting diuretic therapy were strongly related to outcome; a simple score system was constructed by combining these (readily available) clinical parameters and considering each as a risk factor for impaired prognosis. Assessing the prognostic value of the combination of these risk factors showed that patients with three risk factors had a three risk of death or transplantation of ~40%, whereas patients with no risk factors had a 3-year freedom from death or transplantation of 100% as

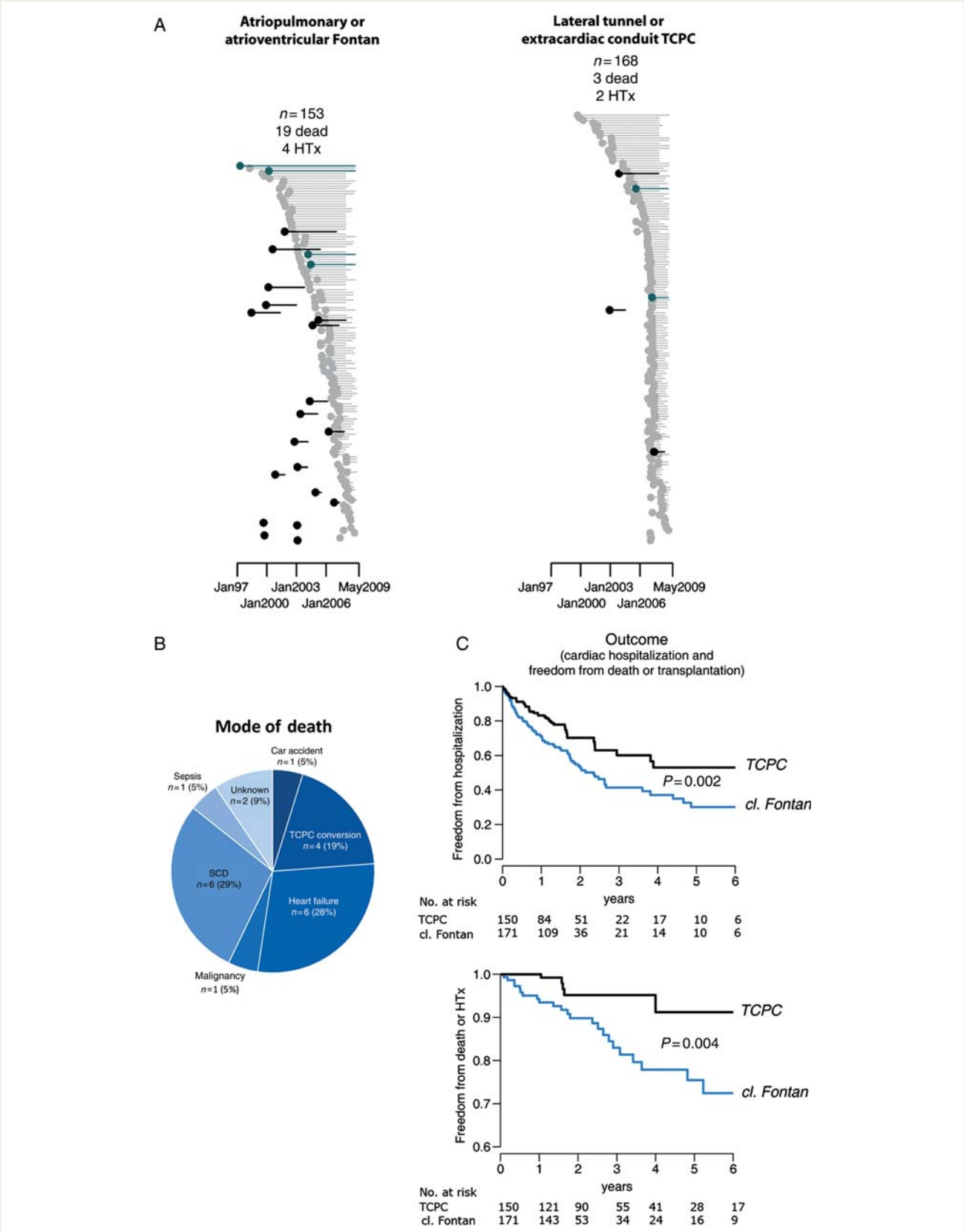

Figure 2 (*A*) Follow-up and outcome in patients after Fontan surgery stratified by type of surgery. The dot marks the begin of follow-up, with the tail representing length of follow-up. Patients who died are in black and those who underwent cardiac transplantation in blue. (*B*) Pie chart of the mode of death providing absolute numbers and percentages. (*C*) Kaplan–Meier plots illustrating freedom from hospitalization (upper panel) and freedom from death or cardiac transplantation (lower panel) in patients with total cavopulmonary anastomosis (TCPC, extracardiac, or lateral tunnel) and those with atriopulmonary or atrioventricular Fontan (cl. Fontan).

Table 2 Univariate Cox proportional-hazard analysis for death or heart transplantation and hospitalization

Variable	Hazard ratio[a] (95% confidence interval)	*P* value	χ^2 value
Death or heart transplantation			
Heart rate reserve (per 10 b.p.m.)	0.828 (0.710–0.965)	**0.016**	5.6
Percentage predicted peakVO_2	0.981 (0.956–1.007)	0.16	2.1
Peak VO_2 (mL/kg/min)	0.959 (0.905–1.015)	0.15	2.1
VE/VCO_2-slope	1.024 (0.991–1.058)	0.15	1.9
Anaerobic threshold (mL/kg/min)	0.971 (0.853–1.105)	0.66	0.2
Age (years)	1.045 (1.002–1.089)	**0.04**	4.0
Age at Fontan completion (years)	1.008 (0.923–1.100)	0.86	0.03
Atriopulmonary/-ventricular Fontan	3.659 (1.388–9.643)	**0.009**	8.6
Clinically relevant arrhythmia	5.982 (2.382–13.158)	**<0.0001**	18.5
Signs and symptoms of heart failure	6.337 (2.799–14.349)	**<0.0001**	22.2
PLE	1.589 (0.482 –5.232)	0.45	0.51
Thrombo-embolic complications	1.213 (0.274–5.382)	0.80	0.06
RV morphology	1.371 (0.520–3.615)	0.53	0.4
Hospitalization			
Heart rate reserve (per 10 b.p.m.)	0.890 (0.822–0.963)	**0.004**	8.2
Percentage predicted peakVO_2	0.973 (0.960–0.986)	**<0.0001**	17.8
Peak VO_2 (mL/kg/min)	0.938 (0.912–0.965)	**<0.0001**	21.2
VE/VCO_2-slope	1.021 (1.003–1.039)	**0.02**	4.9
Anaerobic threshold (mL/kg/min)	0.894 (0.823–0.970)	**0.007**	8.9
Age (years)	1.032 (1.011–1.053)	**0.003**	8.1
Age at Fontan completion (years)	1.044 (1.007–1.081)	**0.02**	4.5
Atriopulmonary/-ventricular Fontan	1.707 (1.167–2.496)	**0.006**	7.8
Clinically relevant arrhythmia	3.621 (2.498–5.250)	**<0.0001**	44.3
Signs and symptoms of heart failure	2.173 (1.496–3.158)	**<0.0001**	15.4
PLE	2.303 (1.292–4.107)	**0.005**	6.4
Thrombo-embolic complications	1.374 (0.583–3.236)	0.47	0.5
RV morphology	1.527 (0.952–2.448)	0.08	2.8

b.p.m., beats per minute; peak VO_2, peak oxygen consumption (mL/kg/min). PLE, protein loosing enteropathy.
[a]Hazard ratios for heart rate reserve, percentage predicted peak oxygen consumption, peak oxygen consumption, and VE/VCO_2-slope are per beat per minute, %, one mL/kg/min, and unit, respectively.
Significant *P*-values are given in bold.

Table 3 Bivariate Cox proportional-hazard analysis for all cause mortality.

Variable	Hazard ratio[a] (95% confidence interval)	*P*-value	Joint χ^2 value
Bivariate analyses			
Heart rate reserve (b.p.m.)	0.976 (0.959–0.994)	**0.01**	18.1
Class I or III AADs[b]	4.0 (1.7–9.7)	**0.002**	
Heart rate reserve (b.p.m.)	0.978 (0.961–0.995)	**0.01**	12.3
Age (years)	1.047 (1.002–1.095)	**0.043**	
Heart rate reserve (b.p.m.)	0.969 (0.952–0.987)	**0.0007**	22.0
ltTCPC or ecTCPC	6.807 (1.986–23.364)	**0.002**	

AADs, antiarrhythmic drugs; b.p.m., beats per minute; ltTCPC and ecTCPC, lateral tunnel total cavopulmonary anastomosis and extracardiac conduit TCPC, respectively.
[a]Hazard ratios for heart rate reserve are per beat per minute.
[b]Classification of antiarrhythmic drugs according to Vaughan Williams.
Significant *P*-values are given in bold.

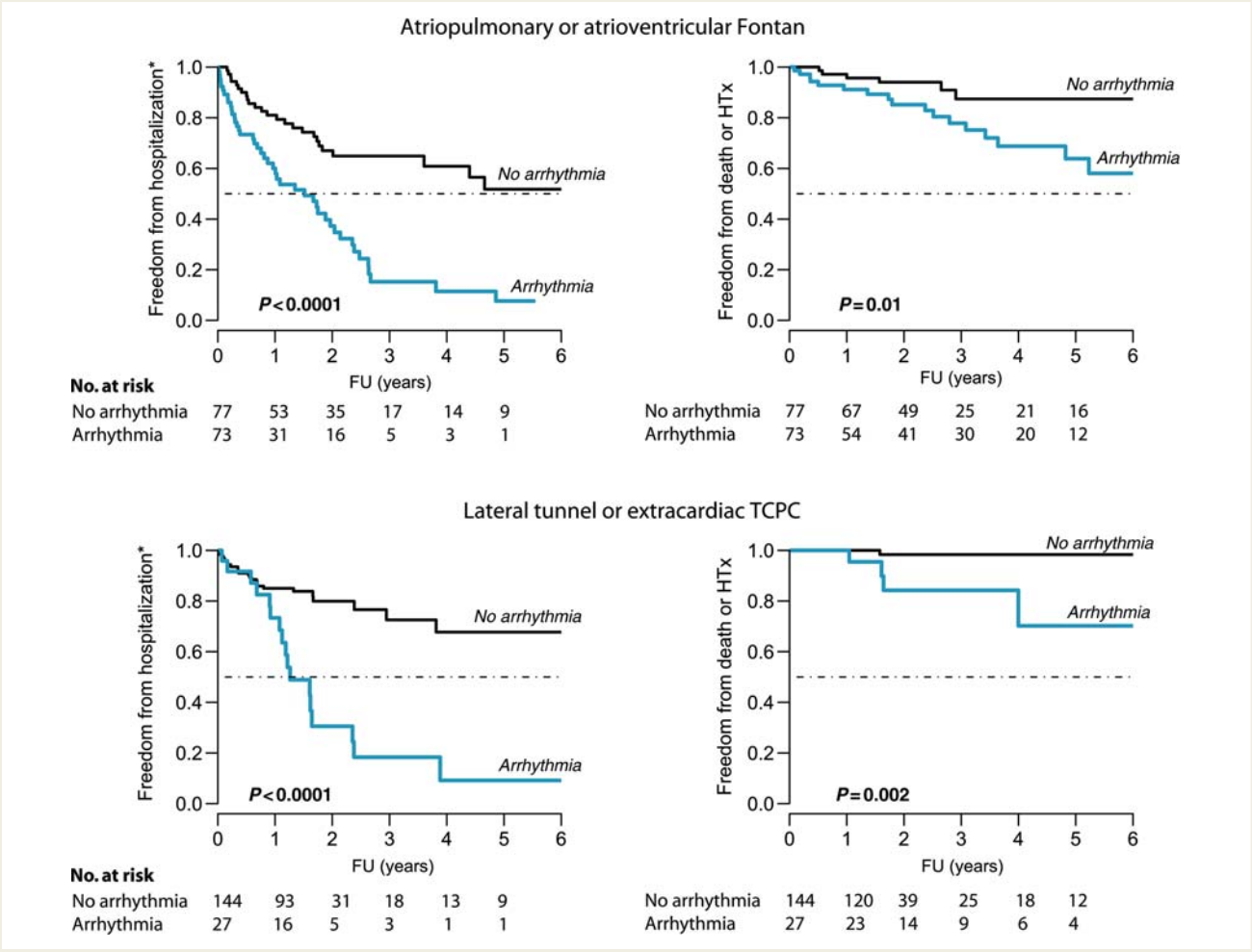

Figure 3 Kaplan–Meier plots for freedom from cardiac-related hospitalization and freedom from death or cardiac transplantation (HTx) in patients with atriopulmonary or atrioventricular Fontan and those with lateral tunnel or extracardiac total cavopulmonary anastomosis according to a history of clinically relevant arrhythmia. Log-rank *P*-values are shown.

illustrated in *Figure 4*. Patients with one or two risk factors had an intermediate risk of death or transplantation. The score was also found to correlate with the risk for cardiac-related hospitalization (*Figure 4*). Random survival forest and rank-hazard analyses were employed to compare the prognostic value of the scoring system with that of parameters of CPET (*Figure 5*). Both methods indicated that the simple clinical score was superior in identifying patients at risk for death or transplantation compared with parameters of CPET. In fact, the random survival forest analysis suggested that the relative prognostic value of percentage predicted peak VO_2 for death or transplantation was only ~1/5 compared with that of the clinical score.

Discussion

The main findings of the study are: (i) peak VO_2 is severely impaired in contemporary Fontan patients, (ii) parameters of exercise testing relate to morbidity in this patient cohort, associated with an increased risk for cardiac-related hospitalization, whereas all assessed parameters of CPET—with the possible exception of heart rate reserve—were unrelated to mortality or cardiac transplantation, and (iii) non-TCPC type of Fontan palliation, a history of clinically relevant arrhythmia, and signs and symptoms of heart failure requiring diuretic treatment emerged as strong markers of morbidity and mortality. A combination of these (simple and readily available) factors was strongly related to outcome and outperformed any measure of CPET in estimating prognosis in the current study.

Previous studies have established that exercise intolerance is prevalent among patients with Fontan palliation.[23,24] This is the first study to assess the association between markers of exercise capacity and outcome in Fontan patients. Although our group has previously shown that parameters of CPET are related to outcome in patients with congenital heart disease in general,[1–3] the prognostic value of CPET in Fontan patients is unknown due to the limited number of Fontan patients included in previous studies. Combining exercise tests performed at four large European centres for adult congenital heart disease allowed us to include a sufficient number of patients and obtain adequate numbers of events to investigate this possible association.

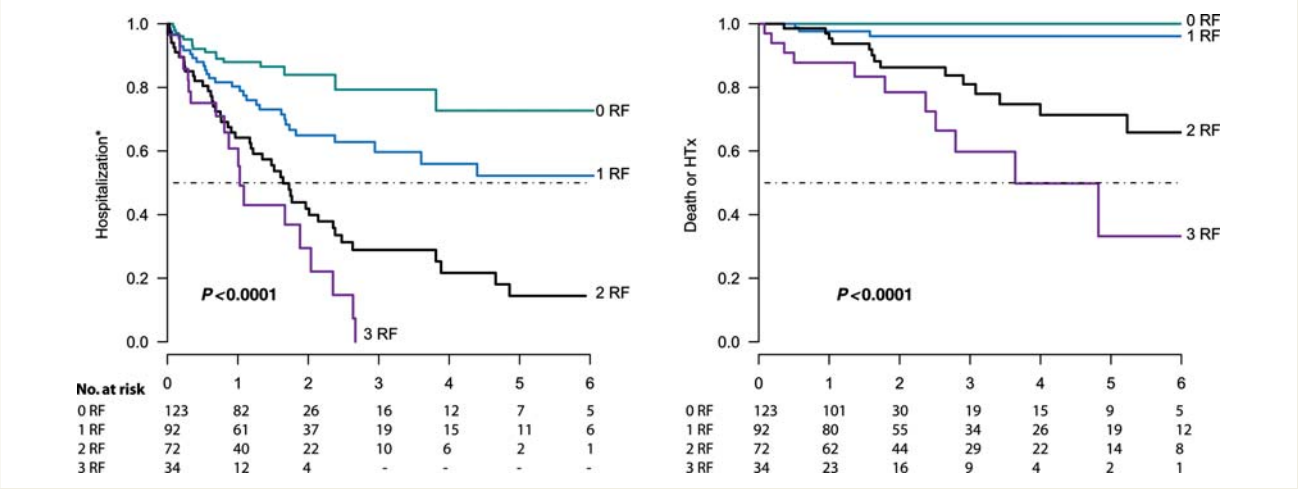

Figure 4 Kaplan–Meier plots according to the number of risk factors defined as non-total cavopulmonary anastomosis type of Fontan surgery, history of clinically relevant arrhythmias, and history of signs and symptoms of heart failure requiring diuretic therapy. Log-rank *P*-values are shown. RF, risk factor as defined above.

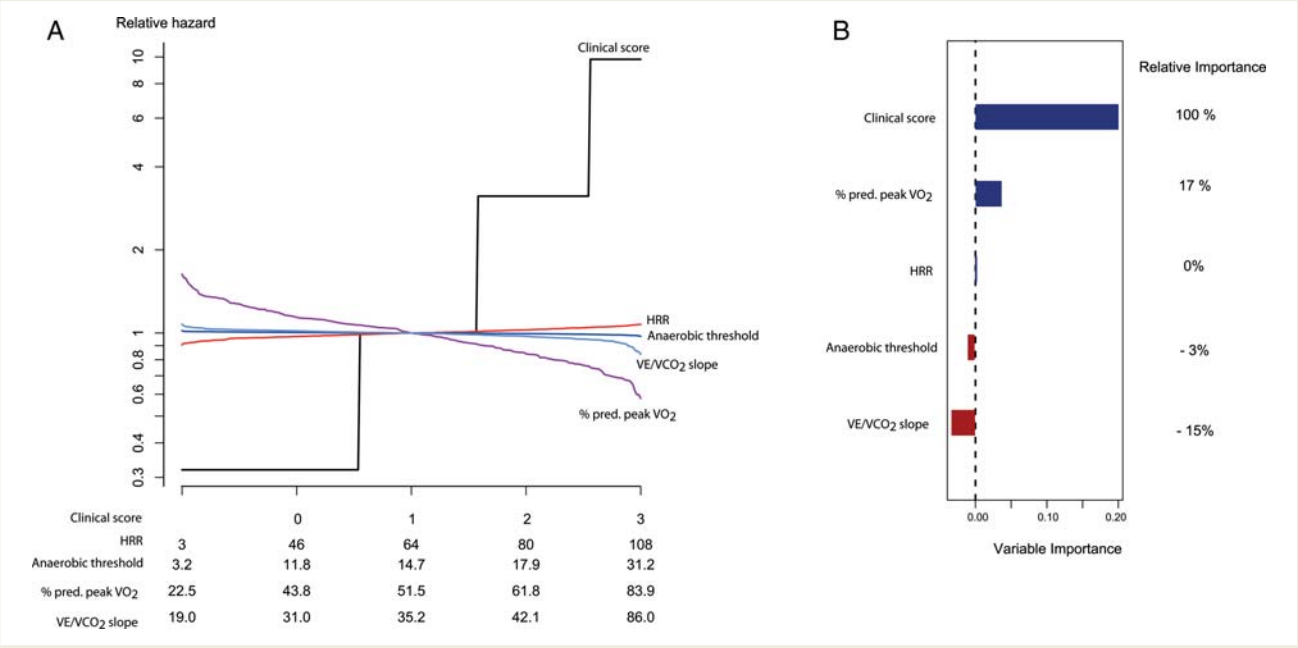

Figure 5 (*A*) Relative hazard plot illustrating the relative predictive value of parameters of the clinical score (defined as non-total cavopulmonary anastomosis type of surgery, history of clinically relevant arrhythmias, and history of signs and symptoms of heart failure requiring diuretic therapy) and parameters of cardiopulmonary exercise testing. The steeper the change in relative hazard over the spectrum of the variable the higher the predictive value of the variable. (*B*) Relative importance of the clinical score and parameters of cardiopulmonary exercise testing in predicting prognosis based on the results of a random survival forest analysis as described in detail by Ishwaran *et al.*[19,20] HRR,heart rate reserve; % pred. peak VO_2, % predicted peak oxygen consumption.

Perhaps surprisingly, no association between peak VO_2, anaerobic threshold, or VE/VCO_2-slope, and survival or cardiac transplantation could be established. We speculate that the inability to adequately increase pulmonary blood flow during exercise limits peak VO_2, whereas VE/VCO_2-slope is affected by increased dead space ventilation and lowering of the chemoreceptor set point for carbon dioxide as reported previously.[25] Thus, the abnormal values of peak VO_2 and VE/VCO_2 do not arise from the usual constellation of ominous pathophysiological abnormalities (such as poor ventricular function and vascular remodelling) but rather

from an intrinsically impaired capacity to increase pulmonary blood flow adequately during exercise, increased dead space ventilation, and lowering of the chemoreceptor set point, limiting the prognostic value of parameters of CPET. This is reminiscent of patients with cyanotic congenital heart disease in whom also no prognostic value of parameters of CPET could be demonstrated in previous studies.[3] Furthermore, some Fontan patients may present with fenestrations and shunt lesions, and right-to-left shunting during exercise may further reduce the prognostic importance of exercise parameters in this setting. In contrast, increase in heart rate during exercise (heart rate reserve) was related to survival, and this association was independent of the use of antiarrhythmic drugs. This is in agreement with a previous study identifying heart rate reserve as a strong prognostic marker in adult congenital heart disease patients, including Fontan patients in a subgroup analysis. We speculate that the prognostic value of heart rate reserve may be related to the fact that unlike the other parameters of exercise testing, heart rate reserve is related to autonomic dysfunction and cardiac arrhythmias.[2,26–28] In fact, cardiac arrhythmias are common after Fontan operation as confirmed by numerous previous studies,[29,30] haemodynamically poorly tolerated,[31] and were identified as a leading cause of death in the current study. In addition, a history of clinically relevant arrhythmia was strongly associated with increased mortality or need for transplantation in our study. However, although significant on Cox proportional-hazard analysis, subsequent analyses employing rank-hazard tests and random survival forests suggested that heart rate reserve may not carry important prognostic information beyond that already available from the medical history and clinical examination.

A striking difference in mortality or need for transplantation was found between patients with TCPC and those with atriopulmonary or atrioventricular Fontan. Thus, the results of the current study disagree with a recently published, single-centre study spanning 25 years of follow-up showing comparable rates of death or transplantation among all types of Fontan patients.[32] The higher rate of mortality/cardiac transplantation in patients with atriopulmonary or atrioventricular Fontan in this study is, however, in agreement with a study by d'Udekem *et al.*[33] In the current study, TCPC patients had significantly fewer cardiac-related hospitalizations and a lower incidence of clinically relevant arrhythmias compared with atriopulmonary or atrioventricular Fontan patients consistent with previous reports.[29,34] Our results support the notion that atriopulmonary or atrioventricular Fontan provides more substrate for atrial arrhythmias and related morbidity and mortality over time. The onset of clinically relevant arrhythmia, generally requiring chronic antiarrhythmic therapy, emerged as an ominous prognostic sign late after Fontan operation in the present study. Due to the study design, we cannot assess the specific impact of antiarrhythmic medication on patient outcome. Whether the onset of clinical arrhythmias necessitating antiarrhythmic therapy was the primary cause or a surrogate for further progression of heart disease, our data suggest that despite therapy with Class I or Class III antiarrhythmic drugs (mainly amiodarone) in many patients, mortality rates were substantial. Further studies are required to assess whether ablation therapy—where applicable—is superior to antiarrhythmic medication and whether timely conversion atriopulmonary or atrioventricular Fontan patients with arrhythmias (with or without arrhythmia-surgery) to TCPC would improve survival.

Various studies have explored risk factors for mortality in patients with single ventricle physiology undergoing Fontan palliations.[32,35–38] The majority of studies, however, focused on risk stratification for Fontan completion or covered long time intervals, during which one or more cardiac operations took place, thus limiting the value of these prognostic data in guiding clinical management. According to current ACC/AHA guidelines, lifelong follow-up is recommended for patients after Fontan operation and this should include a yearly evaluation at a adult congenital heart disease centre (Level of Evidence: C).[39] In addition to clinical examination, electrocardiography, chest x-ray, and echocardiography or magnetic resonance imaging to assess ventricular function, valve regurgitation, and the Fontan circuit, CPET is increasingly employed to assess objective exercise tolerance and to guide therapy. This may be useful, especially as peak VO_2 is an essential component of appropriate exercise prescription and activity guidelines. The results of the current study, however, suggest that extrapolating short-term prognosis directly from the results of a single cardiopulmonary exercise test may be inappropriate and clinicians should be aware of this limitation when using parameters of CPET as part of the decision-making process for referring Fontan patients for transplantation. The current study suggests that a clinical combined prognostic tool, taking into account type of Fontan palliation, history of clinically relevant arrhythmias, and signs and symptoms of heart failure is likely to be superior to parameters of CPET in estimating short-term prognosis. In fact, the results of the current study suggest that the relative prognostic value regarding death or transplantation of clinical information is approximately five times higher than that provided by any measure of CPET. Further studies are required to assess whether longitudinal exercise testing providing information on change in peak VO_2 over time may provide better prognostic information.

Limitations of the study

Patients with atriopulmonary Fontan were significantly older compared with TCPC patients, and despite the fact that bivariate survival analysis suggested type of Fontan surgery to be a prognostic marker independent of age, the older age of atriopulmonary Fontan is likely to account—at least in part—for the worse outcome in this cohort. The number of deaths forming the basis of this report is relatively small and future prospective studies with a longer period of observation and a higher number of clinical events are desirable to validate our report and to provide information on the potential impact of established and evolving therapies on prognosis and symptoms. Furthermore, on a conceptual basis, it is unclear why abnormal parameters of CPET are associated with an increased risk of cardiac-related hospital admission but not death or need for transplantation in the current study. Now that this discrepancy is emerging, further research may be stimulated that could elucidate the mechanisms responsible. Cardiopulmonary exercise testing in this study was performed as part of routine evaluation of Fontan patients. All patients were at tertiary adult congenital heart disease centres, and therefore, it is possible that they may not represent the pattern of adult congenital heart disease that may exist in the community. All four centres have

a policy of performing periodic CPET in all Fontan patients agreeing and able to perform them. Overall, >80–90% of eligible Fontan patients under active follow-up at the centres underwent an exercise test during the study period and were included in this study. Although we cannot exclude the possibility of referral bias to the tertiary centres (potentially accounting for the observed considerable morbidity and mortality), we contend that selection bias within the centres is not likely to represent a major limitation of the current work.

Conclusion

Exercise intolerance is prevalent amongst patients with a Fontan palliation and relates to increased short-term morbidity but not increased mortality or need for cardiac transplantation in our cohort. Non-TCPC type of Fontan palliation, a history of clinically relevant arrhythmia, and signs and symptoms of heart failure were identified as strong prognosticators of morbidity and mortality. A combination of these factors was strongly related to risk of death or transplantation and was far superior to any measure of CPET in assessing outcome in the current study.

Conflict of interest: none declared.

References

1. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, Johansson B, Bouzas B, Mullen MJ, Poole-Wilson PA, Francis DP, Gatzoulis MA. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. *Circulation* 2005;**112**:828–835.
2. Diller GP, Dimopoulos K, Okonko D, Uebing A, Broberg CS, Babu-Narayan S, Bayne S, Poole-Wilson PA, Sutton R, Francis DP, Gatzoulis MA. Heart rate response during exercise predicts survival in adults with congenital heart disease. *J Am Coll Cardiol* 2006;**48**:1250–1256.
3. Dimopoulos K, Okonko DO, Diller GP, Broberg CS, Salukhe TV, Babu-Narayan SV, Li W, Uebing A, Bayne S, Wensel R, Piepoli MF, Poole-Wilson PA, Francis DP, Gatzoulis MA. Abnormal ventilatory response to exercise in adults with congenital heart disease relates to cyanosis and predicts survival. *Circulation* 2006;**113**:2796–2802.
4. Giardini A, Hager A, Lammers AE, Derrick G, Muller J, Diller GP, Dimopoulos K, Odendaal D, Gargiulo G, Picchio FM, Gatzoulis MA. Ventilatory efficiency and aerobic capacity predict event-free survival in adults with atrial repair for complete transposition of the great arteries. *J Am Coll Cardiol* 2009;**53**:1548–1555.
5. Giardini A, Specchia S, Tacy TA, Coutsoumbas G, Gargiulo G, Donti A, Formigari R, Bonvicini M, Picchio FM. Usefulness of cardiopulmonary exercise to predict long-term prognosis in adults with repaired tetralogy of Fallot. *Am J Cardiol* 2007;**99**:1462–1467.
6. Canter CE, Shaddy RE, Bernstein D, Hsu DT, Chrisant MRK, Kirklin JK, Kanter KR, Higgins RSD, Blume ED, Rosenthal DN, Boucek MM, Uzark KC, Friedman AH, Young JK. Indications for Heart Transplantation in Pediatric Heart Disease: A Scientific Statement From the American Heart Association Council on Cardiovascular Disease in the Young; the Councils on Clinical Cardiology, Cardiovascular Nursing, and Cardiovascular Surgery and Anesthesia; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007;**115**:658–676.
7. Bernstein D, Naftel D, Chin C, Addonizio LJ, Gamberg P, Blume ED, Hsu D, Canter CE, Kirklin JK, Morrow WR. Outcome of listing for cardiac transplantation for failed Fontan: a multi-institutional study. *Circulation* 2006;**114**:273–280.
8. Fontan F, Baudet E. Surgical repair of tricuspid atresia. *Thorax* 1971;**26**:240–248.
9. Eicken A, Fratz S, Gutfried C, Balling G, Schwaiger M, Lange R, Busch R, Hess J, Stern H. Hearts late after fontan operation have normal mass, normal volume, and reduced systolic function: a magnetic resonance imaging study. *J Am Coll Cardiol* 2003;**42**:1061–1065.
10. Piran S, Veldtman G, Siu S, Webb GD, Liu PP. Heart failure and ventricular dysfunction in patients with single or systemic right ventricles. *Circulation* 2002;**105**:1189–94.
11. Freedom RM, Hamilton R, Yoo S-J, Mikailian H, Benson L, McCrindle B, Justino H, Williams WG. The Fontan procedure: analysis of cohorts and late complications. *Cardiol Young* 2000;**10**:307–331.
12. Giardini A, Hager A, Napoleone CP, Picchio FM. Natural history of exercise capacity after the Fontan operation: a longitudinal study. *Ann Thorac Surg* 2008;**85**:818–821.
13. Vaughan-Williams E. Classification of Antiarrhythmic Drugs. Sodertal JE: Sweden AD Astra; 1970.
14. Astrand I. Aerobic work capacity in men and women with special reference to age. *Acta Physiol Scand* 1960;**49**(Suppl 169):1–92.
15. Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. *Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications*. Philadelphia: Lippincott Williams & Wilkins; 2004.
16. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1986;**60**:2020–2027.
17. Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. *Biometrics* 2000;**56**:337–344.
18. Cole CR, Foody JM, Blackstone EH, Lauer MS. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. *Ann Intern Med* 2000;**132**:552–555.
19. Ishwaran H, Kogalur UB, Blackstone EH, Lauer MS. Random survival forests. *Ann Appl Stat* 2008;**3**:841–860.
20. Ishwaran H, Kogalur UB. Random Survival Forests for R. *R News* 2007;**7/2**:25–31.
21. Karvanen J, Harrell FE Jr. Visualizing covariates in proportional hazards model. *Stat Med* 2009;**28**:1957–1966.
22. R Development Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria, 2006 ISBN 3-900051-07-0, http://www.Rproject.org.
23. Fredriksen PM, Veldtman G, Hechter S, Therrien J, Chen A, Warsi MA, Freeman M, Liu P, Siu S, Thaulow E, Webb G. Aerobic capacity in adults with various congenital heart diseases. *Am J Cardiol* 2001;**87**:310–314.
24. Weipert J, Koch W, Haehnel JC, Meisner H. Exercise capacity and mid-term survival in patients with tricuspid atresia and complex congenital cardiac malformations after modified Fontan-operation. *Eur J Cardiothorac Surg* 1997;**12**:574–580.
25. Troutman WB, Barstow TJ, Galindo AJ, Cooper DM. Abnormal dynamic cardiorespiratory responses to exercise in pediatric patients after Fontan procedure. *J Am Coll Cardiol* 1998;**31**:668–673.
26. Davos CH, Francis DP, Leenarts MF, Yap SC, Li W, Davlouros PA, Wensel R, Coats AJ, Piepoli M, Sreeram N, Gatzoulis MA. Global impairment of cardiac autonomic nervous activity late after the Fontan operation. *Circulation* 2003;**108**(Suppl. 1):II180–II18–5.
27. Colucci WS, Ribeiro JP, Rocco MB, Quigg RJ, Creager MA, Marsh JD, Gauthier DF, Hartley LH. Impaired chronotropic response to exercise in patients with congestive heart failure. Role of postsynaptic beta-adrenergic desensitization. *Circulation* 1989;**80**:314–323.
28. Ellestad MH. Chronotropic incompetence: the implications of heart rate response to exercise (compensatory parasympathetic hyperactivity?). *Circulation* 1996;**93**:1485–1487.
29. Stamm C, Friehs I, Mayer JE Jr, Zurakowski D, Triedman JK, Moran AM, Walsh EP, Lock JE, Jonas RA, Del Nido PJ. Long-term results of the lateral tunnel Fontan operation. *J Thorac Cardiovasc Surg* 2001;**121**:28–41.
30. Weipert J, Noebauer C, Schreiber C, Kostolny M, Zrenner B, Wacker A, Hess J, Lange R. Occurrence and management of atrial arrhythmia after long-term Fontan circulation. *J Thorac Cardiovasc Surg* 2004;**127**:457–464.
31. Ohuchi H, Miyazaki A, Watanabe T, Yamada O, Yagihara T, Echigo S. Hemodynamic deterioration during simulated supraventricular tachycardia in patients after the Fontan operation. *Int J Cardiol* 2007;**117**:381–387.
32. Khairy P, Fernandes SM, Mayer JE Jr., Triedman JK, Walsh EP, Lock JE, Landzberg MJ. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. *Circulation* 2008;**117**:85–92.
33. d'Udekem Y, Iyengar AJ, Cochrane AD, Grigg LE, Ramsay JM, Wheaton GR, Penny DJ, Brizard CP. The Fontan procedure: contemporary techniques have improved long-term outcomes. *Circulation* 2007;**116**:I-157–I–164.
34. Nurnberg JH, Ovroutski S, Alexi-Meskishvili V, Ewert P, Hetzer R, Lange PE. New onset arrhythmias after the extracardiac conduit fontan operation compared with the intraatrial lateral tunnel procedure: early and midterm results. *Ann Thorac Surg* 2004;**78**:1979–1988.
35. Gentles TL, Mayer JE Jr, Gauvreau K, Newburger JW, Lock JE, Kupferschmid JP, Burnett J, Jonas RA, Castaneda AR, Wernovsky G. Fontan operation in five hundred consecutive patients: factors influencing early and late outcome. *J Thorac Cardiovasc Surg* 1997;**114**:376–391.
36. Giannico S, Hammad F, Amodeo A, Michielon G, Drago F, Turchetta A, Di Donato R, Sanders SP. Clinical outcome of 193 extracardiac Fontan patients: the first 15 years. *J Am Coll Cardiol* 2006;**47**:2065–2073.
37. Knott-Craig CJ, Danielson GK, Schaff HV, Puga FJ, Weaver AL, Driscoll DD. The modified Fontan operation. An analysis of risk factors for early postoperative

death or takedown in 702 consecutive patients from one institution. *J Thorac Cardiovasc Surg* 1995;**109**:1237–1243.
38. Mitchell ME, Ittenbach RF, Gaynor JW, Wernovsky G, Nicolson S, Spray TL. Intermediate outcomes after the Fontan procedure in the current era. *J Thorac Cardiovasc Surg* 2006;**131**:172–180.
39. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham TP Jr, Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP, Webb GD, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Page RL, Riegel B, Tarkington LG, Yancy CW. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2008; **52**:e1–e121.

CARDIOVASCULAR FLASHLIGHT

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Circumferential compression of bilateral ventricles by tuberculous granuloma leading to heart failure

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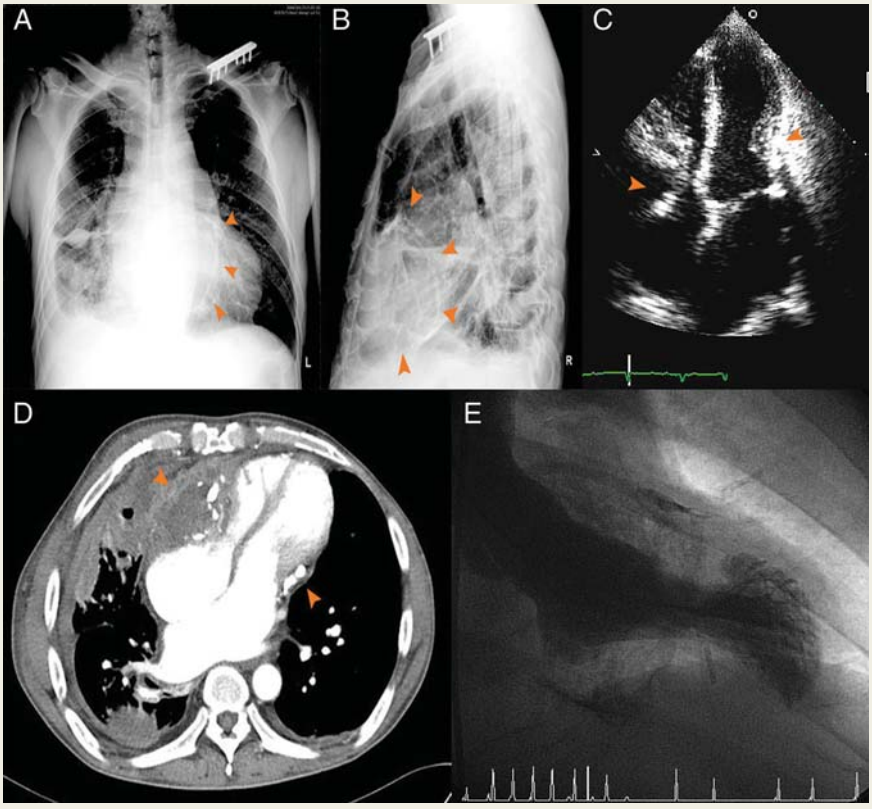

A 52-year-old man presented with exertional dyspnoea, leg oedema, distended jugular veins, and hepatomegaly. Chest radiography showed a right pleural effusion and calcification of pericardium (arrowhead, *Figure A* and *B*). Echocardiography revealed compression of the ventricles by an ill-defined mass at atrioventricular grooves (arrowhead, *Figure C*). Chest computerized tomography (CT) showed heterogeneous mass at right lower lung and anterior mediastinal masses, pressing into lateral walls of the ventricles with dense calcification at pericardium (arrowhead, *Figure D*). Left ventricle (LV) angiography revealed an hourglass-shaped LV during diastolic phase, consistent with the echocardiogram and CT images (*Figure E*). At surgery, severe calcification of the pericardium associated with circumferential encasement of the ventricles by dense masses was found. Extensive pericardiotectomy was performed with mass excision. Histopathological study revealed the masses to be tuberculous granuloma. Postoperative recovery was uneventful with patient reporting a gradual improvement in exertional dyspnoea.

Tuberculous constrictive pericarditis is not uncommon; however, tuberculous granuloma led to compression of LV and heart failure is rare. We demonstrate such a case of heart failure, which is potentially curable by surgery.