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ORIGINAL ARTICLE

New York Heart Association (NYHA) classification in adults with congenital heart disease: relation to objective measures of exercise and outcome

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Aims The New York Heart Association functional classification (NYHA class) is often used to describe the functional capacity of adults with congenital heart disease (ACHD), albeit with limited evidence on its validity in this heterogeneous population. We aimed to validate the NYHA functional classification in ACHD by examining its relation to objective measures of limitation using cardiopulmonary exercise testing (CPET) and mortality.

Methods and results This study included all ACHD patients who underwent a CPET between 2005 and 2015 at the Royal Brompton, in whom functional capacity was graded according to the NYHA classification. Congenital heart diagnoses were classified according to the Bethesda score. Time to all-cause mortality from CPET was recorded in all 2781 ACHD patients (mean age 33.8 ± 14.2 years) enrolled in the study. There was a strong relation between NYHA class and peak oxygen consumption (peak VO2), ventilation per unit in carbon dioxide production (VE/VCO2) slope and the Bethesda classification ($P < 0.0001$). Although a large number of 'asymptomatic' (NYHA class 1) patients did not achieve a 'normal' peak VO2, the NYHA class was a strong predictor of mortality, with an 8.7-fold increased mortality risk in class 3 compared with class 1 (hazard ratio 8.68, 95% confidence interval: 5.26–14.35, $P < 0.0001$).

Conclusion Despite underestimating the degree of limitation in some ACHD patients, NYHA classification remains a valuable clinical tool. It correlates with objective measures of exercise and the severity of underlying cardiac disease, as well as mid- to long-term mortality and should, thus, be into incorporated the routine assessment and risk stratification of these patients.

Keywords Congenital heart diseases • NYHA • Cardiopulmonary exercise test • Prognosis • Mortality

Introduction

Congenital heart disease affects close to 1% of live births. Surgical advances and improvement in medical care have significantly reduced early mortality and led to an exponential growth of the adult congenital heart disease (ACHD) population.[1] Long-term complications are, however, common, with heart failure becoming a major cause of morbidity and mortality, accounting for at least a quarter of all ACHD deaths.[2–7]

Heart failure is a clinical syndrome, characterized by exercise intolerance and/or signs of congestion in the presence of a cardiac condition (congenital or acquired). The use of the New York Heart Association (NYHA) functional classification is recommended in the

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clinical setting to assess the severity of chronic heart failure in patients with left ventricular dysfunction. This subjective evaluation of patients' functional state is important for their diagnosis and management, but also for prognostic reasons.[8–14] Concerns have been raised regarding the use of NYHA classification in ACHD patients. Congenital heart disease is, by definition, present from birth, and patients adapt daily activities to their ability, thus, potentially underestimating and underreporting the severity of physical limitation.[7,11,15,16] Indeed, none of the available heart failure classification grading scales has been validated in ACHD patients, to date.[2,14] In contrast, we and others have reported the prognostic value of cardiopulmonary exercise testing (CPET) in ACHD as a whole or for individual lesions.[11,15,16]

The aim of our study was to validate the NYHA functional classification in ACHD by assessing its relation to objective measures of exercise capacity derived from CPET, and its potential to predict mid- to long-term mortality in these patients.

Methods

Study design and patients

This is a retrospective study of patients with ACHD who underwent a CPET at our centre between January 2005 and May 2015. Patients who had any intervention or clinical deterioration between their clinical appointment and CPET were excluded from the study. Effort-related dyspnoea was graded according to the NYHA functional classification and was based on information obtained from the relevant clinical letter and clinical notes. In our centre, we follow a standard protocol for reporting on consultations, which includes a detailed description of exercise capacity, exercise training, and effort limitation (e.g. distance or time able to walk on the flat, run, or climb stairs). We used such description to classify patients into the NYHA classes presented in this study. For patients who underwent multiple exercise tests during the study period, the first test was recorded and used for the analysis. A principal diagnosis was determined for every patient and classified according to the 32nd Bethesda conference.[17] Cyanotic patients were defined by oxygen saturation less than 90% at rest. Additional clinical data were collected around the time of exercise test, including demographics, pharmacological therapy, brain natriuretic peptide (BNP), and echocardiographic findings. On-going haemodynamic lesions were defined as at least moderate-to-severe systemic and/or subpulmonary obstruction or regurgitation, or a significant intracardiac or extracardiac shunt assessed by echocardiography, cardiac magnetic resonance or invasive catheterization. We also reported as significant haemodynamic lesions baffle obstructions in Mustard/Senning patients and the presence of pulmonary arterial hypertension. Systemic ventricular function was assessed by echocardiography by an experienced echocardiographer blinded to NYHA functional classification and graded in a semi-quantitative manner into normal, mildly, moderately, or severely impaired.[15] Finally, we collected complete data on all-cause mortality and time from CPET within the study period. We included deaths reported by the National Statistics office, an accurate source on mortality information.

Cardiopulmonary exercise test

Cardiopulmonary exercise test was performed on a treadmill according to a modified Bruce protocol, as previously described.[8] Ventilation, oxygen consumption (VO2), carbon dioxide production (VCO2), and ventilation (VE) were measured continuously with simultaneous heart rate and ECG monitoring. Blood pressure was taken at rest, every 3 min, and at maximum effort. Criteria for stopping the test included exhaustion, symptom limitation, drop in blood pressure, or significant ECG changes. Peak VO2 and VE per unit of carbon production (VE/VCO2) were measured. Peak of VO2 was defined according to the European Association of Cardiovascular Prevention and Rehabilitation/American Heart association recommendations.[18] Peak VO2 and VE per unit of carbon production slope was obtained by linear regression analysis of the data acquired throughout the entire period of exercise.

Statistical analysis

Data were summarized as mean ± standard deviation or median and interquartile range for continuous variables, depending on data distribution, and number (%) for categorical variables. In order to assess the reproducibility of the NYHA assigned to ACHD patients, we took a random 100 patients from this cohort who were assessed by two independent observers and, thereafter, estimated Cronbach's coefficient alpha. Comparison of continuous variables between groups was performed using the non-parametric Wilcoxon rank sum test or Kruscal–Wallis test, while categorical variables were compared using the Fisher's exact test. The relation between clinical parameters and all-cause death was assessed using univariate and multivariate Cox proportional hazard regression analysis. For all analyses, a two-tailed *P*-value <0.05 was used as the criterion for statistical significance. Statistical analyses were performed using R version 3.0.1 (The R Foundation for Statistical Computing).

Results

Patients characteristics

In total, 2781 ACHD patients were enrolled in the study and they represented a percentage of patients out of the whole Brompton cohort. Mean age at baseline was 33.8 ± 14.2 years, 1318 (47.4%) were female (*Table 1*). The most common diagnosis was tetralogy of Fallot (TOF) ($n = 552$, 19.8%), followed by aortic coarctation ($n = 260$, 9.3%), pulmonary stenosis ($n = 206$, 7.4%), and ventricular septal defect ($n = 193$, 7.0%). A known genetic abnormality was present in 146 (5%) patients [Di George syndrome ($n = 30$, 21%), Noonan syndrome ($n = 30$, 21%), Marfan syndrome ($n = 26$, 17%), and Down syndrome ($n = 25$, 17%)]. The majority of patients (54.4%) had ACHD of moderate severity, while 90 (3.2%) patients were not classifiable. A systemic right ventricle was present in 216 (7.8%) patients. Cyanosis at rest was present in 151 (5.6%) patients with median oxygen saturation 85 [60–90]%, more frequent in Bethesda Group 3 ($P < 0.0001$). A permanent pacemaker (PPM) or cardiac resynchronization therapy (CRT) device was *in situ* in 6.4%, whereas 1.2% patients had an implantable cardioverter defibrillator (ICD).

Cronbach's alpha for NYHA was 0.87, suggesting good agreement between assessors. The majority of patients (71.1%) were in NYHA functional class 1 at the time of CPET, while a minority were in NYHA 3 (5.6%). Patients in Bethesda 3 group were more likely to be symptomatic (38.4% vs. 25.8% in Bethesda 1 and 2, $P < 0.0001$). Eisenmenger patients were the most symptomatic of all diagnostic subgroups, while the least symptomatic were patients with transposition of the great arteries (TGA) after arterial switch repair (*Figure 1*). Over one half of patients ($n = 1646$, 59.3%) had at least one significant on-going haemodynamic lesion at the time of CPET; the majority of patients had normal systemic ventricular function ($n = 2349$, 84.6%). Patients with moderate or severe systemic ventricular dysfunction were more likely to be in NYHA 2 or 3 ($P < 0.0001$). Baseline BNP was 34 ng/L (range [4–1963] ng/L) with a significant difference

Table 1 Demographic and clinical data according to the Bethesda classification

	All	Bethesda 1	Bethesda 2	Bethesda 3	*P*-value
Patients, *n*	2781	494	1465	732	
Age (year)	33.8 ± 14.2	35.9 ± 16.1	34.9 ± 14.5	30.0 ± 11.2	<0.0001
Female, *n* (%)	1318 (47.4)	224 (45.3)	709 (48.4)	335 (45.8)	0.35
BMI (kg/m^2)	24.4 ± 4.8	24.6 ± 5.0	24.9 ± 4.9	23.2 ± 4.5	<0.0001
Saturation at rest (%)	98.5 [60–100]	98.5 [69–100]	98.5 [80–100]	98.5 [60–100]	<0.0001
Cyanotic patients (Sat < 90%)	151 (5.6)	2 (0.4)	14 (1)	134 (19.2)	<0.0001
Device, *n* (%)					<0.0001
PPM	169 (6.1)	15 (3)	81 (5.5)	71 (9.7)	
CRT	9 (0.3)	1 (0.2)	7 (0.5)	1 (0.1)	
ICD	34 (1.2)	2 (0.4)	20 (1.4)	11 (1.5)	0.18
Medication, *n* (%)					
Beta blockers	289 (10.5)	52 (10.6)	137 (9.5)	73 (10.2)	0.7
Diuretics	187 (6.8)	20 (4.1)	91 (6.3)	71 (9.9)	<0.0001
ARB	105 (3.8)	22 (4.5)	56 (3.9)	19 (2.6)	0.20
ACEi	345 (12.6)	66 (13.4)	142 (9.8)	122 (17)	<0.0001
Antiarrhythmic	183 (6.6)	19 (0.7)	74 (2.7)	86 (3.1)	<0.0001
Functional class, *n* (%)					<0.0001
NYHA 1	1976 (71.1)	377 (76.3)	1086 (74.1)	451 (61.6)	
NYHA 2	650 (23.4)	101 (20.4)	320 (21.8)	208 (28.4)	
NYHA 3	155 (5.6)	16 (3.2)	59 (4)	73 (10)	
BNP level (ng/L)	34 [4–1963]	30 [4–847]	31 [4–1274]	43.5 [8–1963]	0.0022
CPET parameters					
Peak VO2	26.36 ± 9.8	29.4 ± 10.3	26.8 ± 9.3	23.4 ± 9.5	<0.0001
Predicted MVO2 (%)	72.7 ± 22.3	81.9 ± 21.9	75.3 ± 20.7	60.9 ± 20.4	<0.0001
VE/VCO2 slope	33.1 ± 10.7	30.6 ± 7.7	31.6 ± 8.6	37.9 ± 14.4	<0.0001
Echocardiography parameters					
Systemic ventricular function					<0.0001
Normal	2349 (84.6)	432 (87.6)	1317 (90.1)	524 (71.6)	
Mildly impaired	259 (9.3)	39 (7.9)	95 (6.5)	118 (16.1)	
Moderately impaired	108 (3.9)	12 (2.4)	35 (2.4)	58 (7.9)	
Severely impaired	60 (2.2)	10 (2)	15 (1)	32 (4.4)	
Associated lesions	1646 (59.3)	294 (59.5)	929 (63.5)	380 (51.9)	<0.0001

BMI indicates body mass index; NYHA, New York Heart Association; PPM, pacemaker; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; ARB, angiotensin II receptor blockers; ACEi, angiotensin-converting-enzyme inhibitor; antiarrhythmic drugs included amiodarone, flecaine, sotalol and digoxin; CPET, cardiopulmonary exercise testing; RER, peak respiratory ratio; VO2, oxygen consumption; VE/VCO2 slope, ventilation per unit in carbon dioxide production.

between the 3 Bethesda groups (*Figure 2A*). BNP was significantly higher in most symptomatic patients (NYHA 3, median 149 [5–1274] ng/L) compared with remainder ($P < 0.0001$, *Figure 2B*).

Peak VO2 in the overall population was 26.4 ± 9.8 mL/kg/min or 72.7 ± 22.3% of predicted. There was a progressive decline in peak VO2 with increasing Bethesda severity ($P < 0.0001$, *Figure 3A*). The same was true for the VE/VCO2 slope, with patients in the highest anatomic complexity group having significantly higher slopes than the rest (*Table 1*, *Figure 2C*).

Relation between New York Heart Association class and cardiopulmonary exercise parameters

There was a strong relation between functional class and peakVO2, with a progressive decline from functional Class 1 to 3 (*Figure 3B*). Over half (55.2%) of patients in NYHA class 1 had a percent predicted peak VO2 below 80% and were, thus, impaired despite being asymptomatic (*Figure 3B*). Patients in functional class 3 had a markedly reduced peak VO2 of 14.6 ± 5.9 mL/kg/min compared with 29.0 ± 9.1 mL/kg/min in class 1. Patients in functional class 3 also had the highest VE/VCO2 slopes, with two-thirds of patients having a slope > 33 (*Table 2*, *Figure 2D*). Average VE/VCO2 slope was within high normal limits in functional class 1 patients, but one quarter of asymptomatic patients (25.5%) had an abnormal slope > 33. Almost one half of patients in NYHA class 2 (45.3%) had a VE/VCO2 slope >33.

Patients with cyanosis at rest ($n = 151$), in their majority, had complex anatomy (39.7%), Eisenmenger syndrome (21.9%), or Fontan circulation (19.2%). Within the cyanotic group, average peak VO2 was 42.3 ± 13.0% of predicted and VE/VCO2 slope 52.3 ± 18.6. There was no significant relation between NYHA class and peak VO2 or VE/VCO2 slope, with only a trend for the former (*Figure 3C* and *D*).

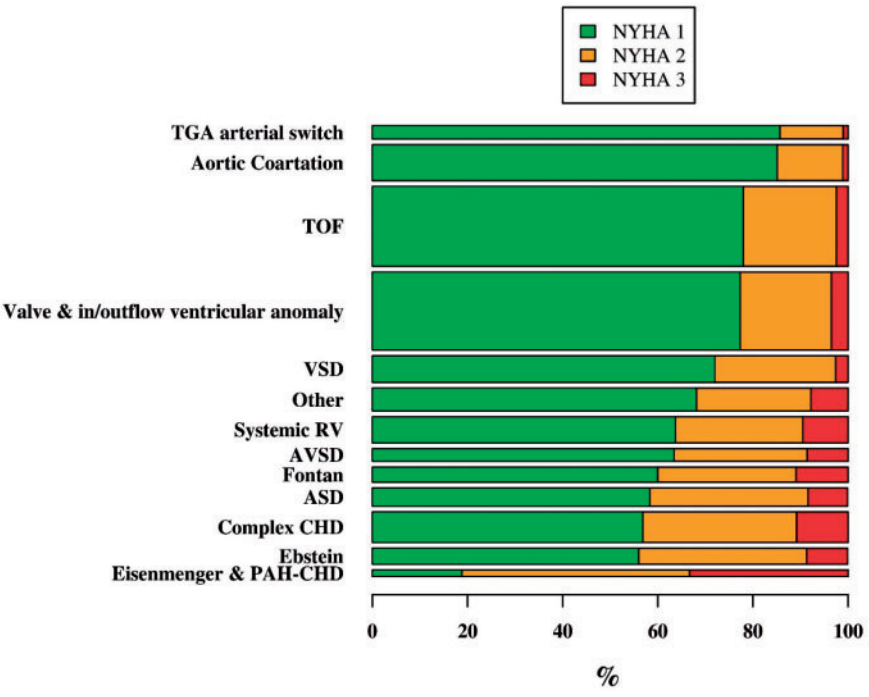

Figure 1 New York Heart Association (NYHA) classification according to major diagnostic groups. Bar width is proportionate to sample size in each group. TGA, transposition of the great arteries; TOF, tetralogy of fallot; VSD, ventricular septal defect; AVSD, atrioventricular septal defect; ASD, atrial septal defect; PAH-CHD, pulmonary arterial hypertension related to congenital heart disease.

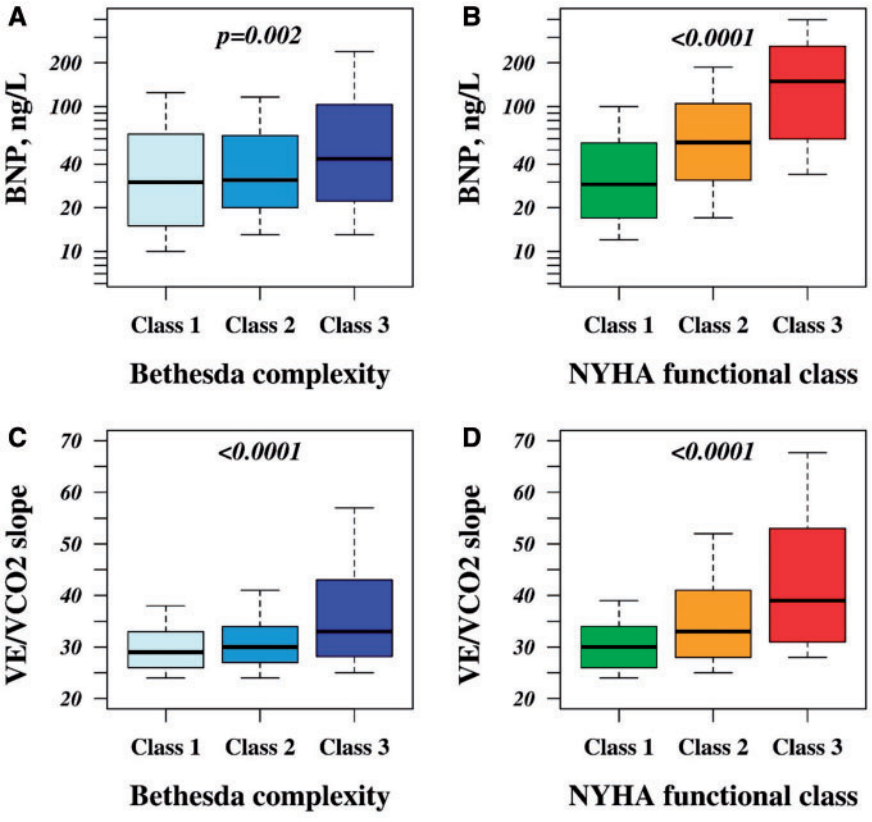

Figure 2 Brain natriuretic peptide (BNP) levels (*A* and *B*) and ventilation per unit in carbon dioxide production (VE/VCO2) slope (*C* and *D*) according to Bethesda classification and New York Heart Association class.

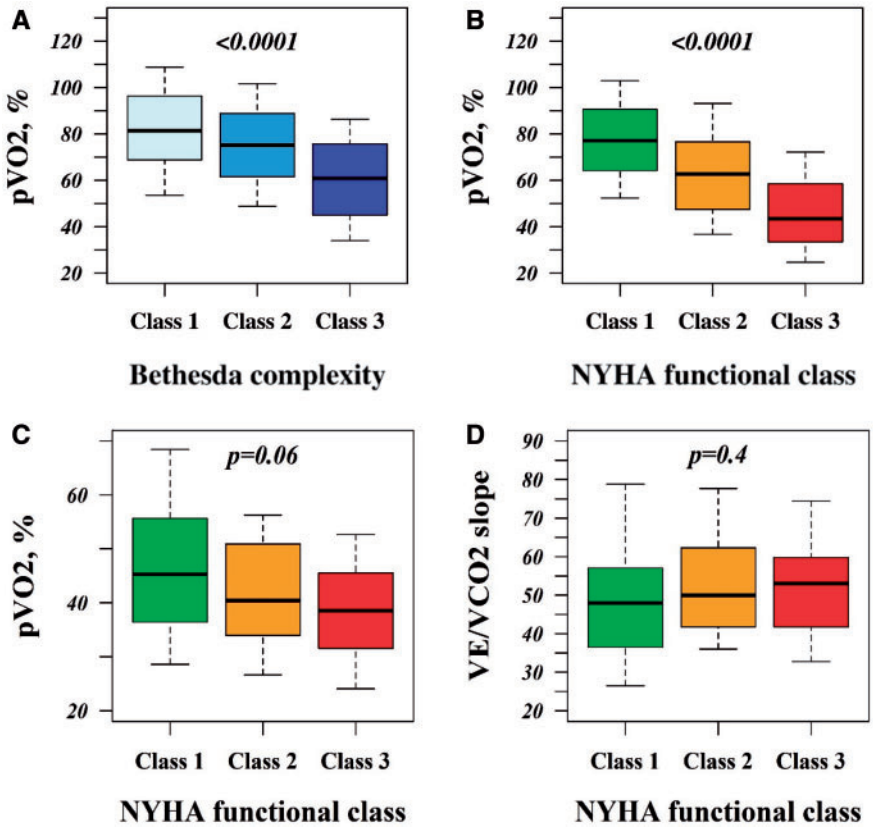

Figure 3 Peak oxygen consumption (VO2) (*A–C*) and ventilation per unit in carbon dioxide production (VE/VCO2) slope (*D*) according to Bethesda classification (*A*) and New York Heart Association functional class (*B–D*) in all adult congenital heart disease (ACHD) patients (*A* and *B*) and cyanotic ACHD patients only (*C* and *D*).

Correlation between New York Heart Association functional class and mortality

At a median follow-up of 4.7 years (interquartile range 2.4–7.1) from index CPET, 99 (3.6%) ACHD patients died. There was a strong relation between NYHA functional class and death, with a 2.5-fold increased mortality risk in class 2 and 8.7-fold in class 3 compared with class 1 [hazard ratio (HR) 2.50, 95% confidence interval (95% CI): 1.58–3.95, $P < 0.0001$ and HR 8.68, 95%CI: 5.26–14.35, $P < 0.0001$, *Figure 4A*] and was also true in patients with cyanosis at rest (*Figure 4B*). Furthermore, there was a significant difference in the risk of death between groups 2 and 3 in the overall ACHD population (HR 3.47, 95% CI: 2.08–5.81, $P < 0.0001$). NYHA class remained a strong predictor of death even when adding age to the model (class 2 $P = 0.001$, class 3 $P < 0.0001$, age $P < 0.0001$). Indeed, NYHA functional class remained a strong and independent predictor of death, when included in a stepwise multivariate model with age, sex, cyanosis, systemic/sub-pulmonary ventricular function, and Bethesda complexity class (*Table 3*). When adding percentage predicted peak VO2, the VE/VCO2 slope and defect complexity to the model with NYHA class, functional class 3 remained a predictor of death ($P = 0.001$) with peak VO2 ($P < 0.0001$), but not VE/VCO2 slope, functional class 2 or defect complexity. The relation between NYHA class and mortality remained largely unaffected when adjusted for BNP concentration ($P = 0.002$ and <0.0001 for classes 2 and 3, respectively).

Discussion

Our data shows NYHA classification to be a valid method for classifying ACHD patients according to functional limitation, as it relates closely to objective measures of exercise capacity, such as peak VO2 and the VE/VCO2 slope, although it may underestimate true limitation in less symptomatic patients. NYHA class also relates to the severity of underlying congenital heart disease, and its strong relation to mortality makes it a simple prognostic tool in clinical practice.

It has been suggested that NYHA functional classification should be used with caution in ACHD, as it tends to underestimate the degree of limitation in patients with long-standing disease who have adapted chronically their lifestyle to ability.[15] Our data supports this notion, with over one half of 'asymptomatic' patients having a reduced peak VO2 (*Figure 3B*). However, our analysis also confirms that NYHA class has important prognostic implications for significantly limited patients (NYHA class 3), while it may be less sensitive in identifying patients at risk within the less symptomatic.[15] Indeed, we observed a mortality that appears higher than expected amongst

Table 2 Clinical, CPET, and echocardiography data according to NYHA classification

	All	NYHA 1	NYHA 2	NYHA 3	*P*-value
Age (year)	33.8 ± 14.2	31.8 ± 13.0	37.4 ± 15.3	43.8 ± 16.8	<0.0001
Female (%)	1318 (47.4)	853 (43.2)	377 (58)	88 (56.8)	<0.0001
BMI (kg/m^2)	24.4 ± 4.8	24.2 ± 4.5	24.9 ± 5.5	25.0 ± 5.8	0.0377
Saturation at rest (%)	98.5 [60–100]	98.5 [74–100]	98.5 [63–100]	97 [60–100]	<0.0001
Cyanotic patients (sat < 90%)	151 (5.6)	44 (2.3)	67 (10.7)	40 (27.2)	<0.0001
Bethesda classification, *n* (%)					
Bethesda 1	494 (18.4)	377 (19.7)	101 (16.1)	16 (10.8)	<0.0001
Bethesda 2	1465 (54.4)	1086 (56.7)	320 (50.9)	59 (39.9)	
Bethesda 3	732 (27.2)	451 (23.6)	208 (33.1)	73 (49.3)	
BNP level (ng/L)	34 [4–1963]	29 [4–1780]	56.5 [8–1963]	149 [5–1274]	<0.0001
CPET parameters					
Peak VO2	26.4 ± 9.8	29.0 ± 9.1	21.0 ± 7.9	14.6 ± 5.9	<0.0001
Predicted MVO2 (%)	72.7 ± 22.3	77.61 ± 20.24	63.7 ± 22.0	46.9 ± 19.3	<0.0001
VE/VCO2 slope	33.1 ± 10.7	31.1 ± 8.2	36.4 ± 12.8	44.4 ± 17.5	<0.0001
Echocardiography parameters					
Systemic ventricular function					<0.0001
Normal	2349 (84.6)	1733 (87.8)	510 (78.5)	106 (69.3)	
Mildly impaired	259 (9.3)	163 (8.3)	78 (12)	18 (11.8)	
Moderately impaired	108 (3.9)	55 (2.8)	38 (5.8)	15 (9.8)	
Severely impaired	60 (2.2)	22 (1.1)	24 (3.7)	14 (9.2)	
Sub pulmonary ventricular function					<0.0001
Normal	2133 (82)	1597 (84.9)	452 (76.2)	84 (66.1)	
Mildly impaired	313 (12)	211 (11.2)	85 (14.3)	17 (13.4)	
Moderately impaired	134 (5.2)	67 (3.6)	48 (8.1)	19 (15)	
Severely impaired	20 (0.8)	5 (0.3)	8 (1.3)	7 (5.5)	
Associated lesions	1646 (59.3)	1113 (56.4)	425 (65.4)	108 (70.1)	<0.0001

BMI indicates body mass index; NYHA, New York Heart Association; CPET, cardiopulmonary exercise testing; RER, peak respiratory ratio; VO2, oxygen consumption; VE/VCO2 slope, ventilation per unit in carbon dioxide production.

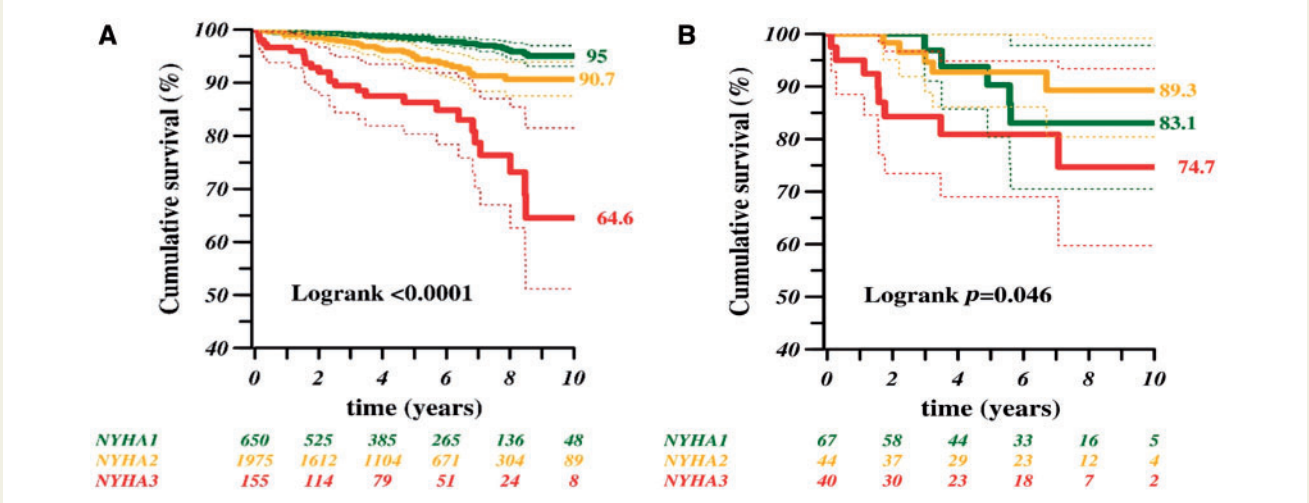

Figure 4 Kaplan–Meier survival curves according to New York Heart Association (NYHA) classification in all adult congenital heart disease (ACHD) (*A*) and cyanotic patients only (*B*).

Table 3 Predictors of mortality in ACHD patients (multivariable analysis)

Functional class	HR (95% CI)	*P*-value
Class 1	Ref	Ref
Class 2	1.93 (1.17–3.17)	0.009
Class 3	3.72 (2.01–6.90)	<0.0001
Age (years)	1.04 (1.02–1.05)	<0.0001
Sex (male)	1.40 (0.91–2.18)	0.13
Systemic ventricular function		
Normal	Ref	Ref
Mildly impaired	2.05 (1.16–3.63)	0.01
Moderately impaired	4.75 (2.71–8.33)	<0.0001
Severely impaired	4.86 (2.27–10.40)	<0.0001
Cyanosis at rest	2.48 (1.40–4.42)	0.002

ACHD, adult congenital heart disease; 95% CI, 95% confidence interval.

the relatively young cohort of ACHD patients in NYHA class 1 (average age 31.8 years, 5% mortality at 10 years, *Figure 4A*). Our paper went beyond the observations by Diller *et al.*[7] by assessing the relation between NYHA and objective measures of exercise capacity, as well as BNP, in a large ACHD population. The strong relation observed between NYHA class and established prognostic markers, such as peak VO2, VE/VCO2 slope, and BNP, provide support for the routine use of the NYHA classification in the clinical setting as a simple but powerful marker of disease severity. Our data, however, suggest that NYHA is more than just a surrogate of exercise capacity, providing prognostic information independent of the above parameters.

The NYHA functional classification relies heavily on the concept of 'ordinary physical activities', which are not well defined and can differ between individuals, depending on their health status, education, upbringing, and personal preference. It is noteworthy that almost one half of patients with atrial septal defects were symptomatic. While this may appear surprising for such a 'simple' lesion, these patients are typically much older at presentation compared with patients with other congenital defects and are, hence, more likely to be impaired and have co-morbidity compared with younger cohorts. Moreover, symptoms typically appear late in these patients who are otherwise asymptomatic for decades prior to presentation, as opposed to other congenital cohorts who are limited since childhood and may underreport symptoms. By definition, congenital heart disease is present from birth and many patients adapt their ordinary activities to their ability, thus, not being aware of under-reporting their functional limitations. Moreover, in the past, cardiologists had been reluctant to encourage ACHD patients to strenuous exercise, resulting in limited physical activity, physical deconditioning and, in some cases, obesity. In such patients, who are not physically active on a regular basis, care should be taken when applying and interpreting the NYHA classification. The use of standard questionnaires, including landmarks (e.g. ability to walk from one department to another, from the local train or metro station to the hospital, etc.) may help improve the physician's ability to detect exercise intolerance and, thus, better classify the patients functional class. It is also important to remember that NYHA classification relies on subjective perception of symptoms, which also depends on factors, such as levels of acceptance of the disease, anxiety or depression, and overall quality of life.[19–21] Doubts have been cast on the ability of physicians to correctly implement the NYHA classification. It has been demonstrated that even experienced physicians tend to use a free interpretation of the NYHA classification, rather than strictly adhering to its definition.[19–22] We submit that correctly applying and interpreting the NYHA classification enhances its value in the clinical setting.

Exercise limitation is a common feature of cardiovascular disease and can be multifactorial. Exercise intolerance in ACHD occurs for a variety of reasons, relating not only to the underlying CHD, but also to associated comorbidity (e.g. pulmonary vascular or other disease, skeletal abnormalities, detraining and muscle wasting, anaemia etc.).[14] Nevertheless, exercise intolerance is closely related to the severity of underlying cardiovascular condition, both in heart failure and ACHD and is, thus, a strong predictor of outcome. Objective markers of exercise limitation, such as the peak VO2, heart rate reserve, and VE/VCO2 slope on CPET have been shown to be strong and independent predictors of mortality in ACHD and should be periodically employed for risk-stratifying patients and determining the type and timing of therapies and intervention.[8,15,16,23–25] The close correlation between NYHA class and CPET parameters in the present study supports the value of NYHA classification as a simple additional prognostic tool, but not a substitute for CPET.

While there was a significant difference in age between NYHA classes, the relation between NYHA class and mortality was independent of age and other clinical and exercise parameters. With the exponential growth in the number of ACHD patients, frequent CPET may not be possible in every setting. Moreover, NYHA class may carry additional prognostic information, as symptoms reported by patients are not confined to exercise intolerance. Indeed, while the NYHA class is not a quality of life index, it has been shown to correlate closely to quality of life scores and may provide a global view of the overall patient status.[26,27] We submit, that the NYHA class remains a valuable tool and should be regularly reported on each clinical visit and integrated to other clinical parameters and prognostic scores.

Study limitations

This is a single-centre retrospective study but, nevertheless, representative of patients followed in tertiary settings with moderately complex CHD. While inclusion of NYHA class 4 in the survival analysis would have been interesting, this study focused on patients who had undergone a CPET and, thus, patients with functional class 4 were excluded. While this referral bias may have affected the estimated prevalence of functional limitation in our population, the relation between functional class and outcome is unlikely to have been affected. Future prospective studies may shed additional light on the prognostic value of functional classification in ACHD, including asymptomatic patients.

Conclusion

Despite certain limitations, NYHA classification remains a valuable clinical tool in ACHD. It correlates with objective measures of exercise capacity and mid- to long-term mortality, and should, thus, be routinely assessed and reported.

Conflict of interest: A.K., K.D., and M.A.G. from the Royal Brompton Hospital have received unrestricted educational and research grants and acted as consultants for Bayer, Pfizer, Actelion, and GSK. Others have no relevant conflict of interests.

References

1. Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. Congenital heart disease in the general population changing prevalence and age distribution. *Circulation* 2007;**115**:163–172.
2. Stout KK, Broberg CS, Book WM, Cecchin F, Chen JM, Dimopoulos K, Everitt MD, Gatzoulis M, Harris L, Hsu DT, Kuvin JT, Law Y, Martin CM, Murphy AM, Ross HJ, Singh G, Spray TL; American Heart Association Council on Clinical Cardiology, Council on Functional Genomics and Translational Biology, and Council on Cardiovascular Radiology and Imaging. Chronic heart failure in congenital heart disease: a scientific statement from the American Heart Association. *Circulation* 2016;**133**:770–801.
3. Mackie AS, Pilote L, Ionescu-Ittu R, Rahme E, Marelli AJ. Health care resource utilization in adults with congenital heart disease. *Am J Cardiol* 2007;**99**:839–843.
4. Opotowsky AR, Siddiqi OK, Webb GD. Trends in hospitalizations for adults with congenital heart disease in the U.S. *J Am Coll Cardiol* 2009;**54**:460–467.
5. O'Leary JM, Siddiqi OK, Ferranti S. D, Landzberg MJ, Opotowsky AR. the changing demographics of congenital heart disease hospitalizations in the United States, 1998 through 2010. *JAMA* 2013;**309**:984–986.
6. Zomer AC, Uiterwaal CSPM, Velde ET. V D, Tijssen JGP, Mariman ECM, Verheugt CL, Vaartjes I, Pieper PG, Meijboom FJ, Grobbee DE, Mulder BJM. Mortality in adult congenital heart disease: are national registries reliable for cause of death? *Int J Cardiol* 2011;**152**:212–217.
7. Diller G-P, Kempny A, Alonso-Gonzalez R, Swan L, Uebing A, Li W, Babu-Narayan S, Wort SJ, Dimopoulos K, Gatzoulis MA. Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a large tertiary centre. *Circulation* 2015;**132**:2118–2125.
8. Dimopoulos K, Okonko DO, Diller G-P, 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.
9. Trojnarska O, Gwizdała A, Katarzyński S, Katarzyńska A, Szyszka A, Lanocha M, Grajek S, Kramer L. Evaluation of exercise capacity with cardiopulmonary exercise test and B-type natriuretic peptide in adults with congenital heart disease. *Cardiol J* 2009;**16**:133–141.
10. Kehmeier ES, Sommer MH, Galonska A, Zeus T, Verde P, Kelm M. Diagnostic value of the six-minute walk test (6MWT) in grown-up congenital heart disease (GUCH): comparison with clinical status and functional exercise capacity. *Int J Cardiol* 2016;**203**:90–97.
11. Kempny A, Dimopoulos K, Uebing A, Moceri P, Swan L, Gatzoulis MA, Diller G-P. Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life–single centre experience and review of published data. *Eur Heart J* 2012;**33**:1386–1396.
12. Madsen BK, Hansen JF, Stokholm KH, Brøns J, Husum D, Mortensen LS. Chronic congestive heart failure. Description and survival of 190 consecutive patients with a diagnosis of chronic congestive heart failure based on clinical signs and symptoms. 1994;**15**:303–310.
13. Holland R, Rechel B, Stepien K, Harvey I, Brooksby I. Patients' self-assessed functional status in heart failure by New York Heart Association class: a prognostic predictor of hospitalizations, quality of life and death. *J Card Fail* 2010;**16**:150–156.
14. Ross HJ, Law Y, Book WM, Broberg CS, Burchill L, Cecchin F, Chen JM, Delgado D, Dimopoulos K, Everitt MD, Gatzoulis M, Harris L, Hsu DT, Kuvin JT, Martin CM, Murphy AM, Singh G, Spray TL, Stout KK. Transplantation and mechanical circulatory support in congenital heart disease a scientific statement from the American Heart Association. *Circulation* 2016;**133**:802–820.
15. Diller G-P, 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.
16. Inuzuka R, Diller G-P, Borgia F, Benson L, Tay ELW, Alonso-Gonzalez R, Silva M, Charalambides M, Swan L, Dimopoulos K, Gatzoulis MA. Comprehensive use of cardiopulmonary exercise testing identifies adults with congenital heart disease at increased mortality risk in the medium term. *Circulation* 2012;**125**:250–259.
17. Webb GD, Williams RG. Care of the adult with congenital heart disease: introduction. *J Am Coll Cardiol* 2001;**37**:1166.
18. Guazzi M, Adams V, Conraads V, Halle M, Mezzani A, Vanhees L, Arena R, Fletcher GF, Forman DE, Kitzman DW, Lavie CJ, Myers J; European Association for Cardiovascular Prevention & Rehabilitation, American Heart Association. EACPR/AHA scientific statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation* 2012;**126**:2261–2274.
19. Huff CM, Turer AT, Wang A. Correlations between physician-perceived functional status, patient-perceived health status, and cardiopulmonary exercise results in hypertrophic cardiomyopathy. *Qual Life Res* 2013;**22**:647–652.
20. Berghammer M, Karlsson J, Ekman I, Eriksson P, Dellborg M. Self-reported health status (EQ-5D) in adults with congenital heart disease. *Int J Cardiol* 2013;**165**:537–543.
21. Raphael C, Briscoe C, Davies J, Ian Whinnett Z, Manisty C, Sutton R, Mayet J, Francis DP. Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. *Heart* 2007;**93**:476–482.
22. Rostagno C, Galanti G, Comeglio M, Boddi V, Olivo G, Gastone Neri Serneri G. Comparison of different methods of functional evaluation in patients with chronic heart failure. *Eur J Heart Fail* 2000;**2**:273–280.
23. Francis DP, Shamim W, Davies LC, Piepoli MF, Ponikowski P, Anker SD, Coats AJ. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO(2) slope and peak VO(2). *Eur Heart J* 2000;**21**:154–161.
24. Myers J, Oliveira R, Dewey F, Arena R, Guazzi M, Chase P, Bensimhon D, Peberdy MA, Ashley E, West E, Cahalin LP, Forman DE. Validation of a cardiopulmonary exercise test score in heart failure. *Circ Heart Fail* 2013;**6**:211–218.
25. Russell SD, Saval MA, Robbins JL, Ellestad MH, Gottlieb SS, Handberg EM, Zhou Y, Chandler B. HF-ACTION Investigators. New York Heart Association functional class predicts exercise parameters in the current era. *Am Heart J* 2009;**158**:S24–S30.
26. Apers S, Kovacs AH, Luyckx K, Thomet C, Budts W, Enomoto J, Sluman MA, Wang J-K, Jackson JL, Khairy P, Cook SC, Chidambarathanu S, Alday L, Eriksen K, Dellborg M, Berghammer M, Mattsson E, Mackie AS, Menahem S, Caruana M, Veldtman G, Soufi A, Romfh AW, White K, Callus E, Kutty S, Fieuws S, Moons P. APPROACH-IS consortium and ISACHD. Quality of life of adults with congenital heart disease in 15 countries: evaluating country-specific characteristics. *J Am Coll Cardiol* 2016;**67**:2237–2245.
27. Amedro P, Basquin A, Gressin V, Clerson P, Jais X, Thambo J-B, Guerin P, Cohen S, Bonnet D. Health-related quality of life of patients with pulmonary arterial hypertension associated with CHD: the multicentre cross-sectional ACHILLE study. *Cardiol Young* 2016;**26**:1250–1259.