Haemodynamics in children with a Fontan circulation: effects of afterload reduction

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Chapter 2

Research design and data collection

sAFE trial

The sAFE-trial, full-title: "ACE inhibition in Fontan patients: its effect on body fluid regulation", was performed at the Leiden University Medical Centre (LUMC) between July 2017 and October 2019. Data collection took place at different outpatient clinics of the departments of paediatrics, neurology, and cardiology. The study was approved by the Medical Ethics Committee of the LUMC (P 17.045) and by the Central Committee on research involving human subjects in the Netherlands (CCMO), as it concerned a prospective intervention study in children. Furthermore, the study was registered in the Dutch Trial registry (NL6415; NTR6591).

Study population

Fontan patients

Patients between 8 to 18 years of age with a univentricular heart after Fontan palliation who had a regular clinical follow-up at one of the outpatient clinics of the Centre for Congenital Heart Disease Amsterdam-Leiden (CAHAL), consisting of the LUMC and the Amsterdam University Medical Centres (Amsterdam UMC, location Boelelaan and Meibergdreef), were included in the study. Patients with pre-existent ACE-inhibitor use and those who had difficulties to follow instructions or were unable to exercise were excluded from the study.

Patients who were eligible for the study were asked to participate via telephone or in person when they visited one of the outpatient's clinics for a routine clinical follow-up. At least one of the two visits, and most often the follow-up visit, was part of a regular clinical follow-up.

Descriptive characteristics of the patients who participated in the study can be found in Table 1. Because often patients receive ACE-inhibitors when they have systolic ventricular dysfunction, all patients included in this study had a moderate-good systolic ventricular function. Furtzhermore, as we included paediatric patients, all patients had been operated with the latest surgical techniques, and all had received a total cavopulmonary connection with an extra cardiac conduit. As a result of our inclusion criteria, we were able to study a homogenous group of Fontan patients.

Healthy controls

Healthy children between 8 to 18 years of age were recruited to take part in the study to serve as controls. Healthy controls were recruited through advertisement at local schools in the surrounding of the LUMC, advertisement at the local science

day of the LUMC and posters in the CORPUS museum in Oegstgeest. Medication use or chronic diseases were exclusion criteria. Descriptive characteristics of the healthy controls are depicted in Table 1.

Informed consent

Written informed consent was obtained from all participants or their parents or legal guardians.

Table 1. Descriptive characteristics

Characteristics	Fontan patients (N=36)	Controls (N=35)
Age (years)	14.0 [12.7-16.6]	12.8 [11.1-15.5]
Males (N,%)	23 (56.1)	18 (43.9)
Height (cm)	163.0 (14.1)	160.8 (13.5)
Weight (kg)	51.4 [42.8-60.3]	46.2 [37.0-56.9]
BSA (m^2)	1.55 (0.3)	1.46 (0.27)
Diagnosis (N,%)		
Tricuspid atresia	9 (25.0)	
Pulmonary atresia	2 (5.6)	
Double inlet left ventricle	5 (13.9)	
Double outlet right ventricle	1 (2.8)	
Hypoplastic left heart syndrome	8 (22.2)	
Unbalanced atrioventricular septum defect	4 (11.1)	
Other	7 (19.4)	
Main ventricle (N;%)		
Left	21 (58.3)	
Right	12 (33.3)	
Indifferent	3 (8.3)	
Age at Glenn operation (years)	0.52 [0.38-0.79]	
Age at Fontan operation (years)	3.2 (0.7)	
Patent Fenestration (N,%)	1 (3.0)	
Pacemaker (N,%)	1 (2.8)	
NT-pro BNP (ng/L)	80.2 [48.0-131.3]	
Cardiac medications (N, %)		
Acetylsalicylic acid	34 (94.4)	
Coumarin derivative	2 (5.9)	
β-blocker	1 (2.8)	
Diuretics	1 (2.8)	

Data expressed as n (%), mean (±SD), and median [Q1-Q3].
BSA= body surface area; NT-pro BNP= N-terminal pro brain natriuretic peptide.

Study design

This study consisted of a cross-sectional and prospective intervention study. For the cross-sectional study, several baseline cardiovascular measurements were compared between Fontan patients and healthy controls. For the prospective intervention study, several cardiovascular measurements measured before and after a three-month enalapril treatment in Fontan patients were compared. Healthy controls were not treated with enalapril.

Figure 1A depicts the timeline of the protocol per visit for the different groups. For both groups, Fontan patients and healthy controls, the visit started at the paediatric outpatient clinic with measuring weight and length, and they were asked about their medication use and if they ever had experienced syncope. Then, electrodes of the VU-AMS monitoring system, measuring electro- (ECG) and impedance cardiogram (ICG), were attached, and connected to the device which the participant could wear with an added belt. Thereafter, participants were relocated to the neurology department for a fluid challenge, which took on average 90 minutes. After the fluid challenge, the in-hospital part of the study was completed for the healthy controls, while Fontan patients usually had a break before going to the paediatric outpatient clinic for a blood test and the cardiology department for an exercise test. As adequate reference values of exercise parameters of healthy children exist, cardiopulmonary exercise tests were not performed in healthy controls.

At the end of hospital visit all participants went home wearing the VU-AMS device, which they could detach after 24 hours from start of the measurement. The device could be sent back the next day by mail using a return envelope which the participants received during their hospital visit.

Fluid challenge:

Figure 1B shows the protocol of the fluid challenge. All participants were placed on a tilt table in supine position to measure baseline parameters. First, a thorough echocardiographic assessment was performed. Then, all devices which would measure different parameters continuously were positioned and connected consecutively. These consisted of an arterial cerebral blood flow registration, pulse oximetry, capnography, and blood pressure measurements by means of the Finapress. The VU-AMS device was already connected at the paediatric outpatient

clinic. When everything was connected, a 4-minute baseline registration took place (first light blue marked period in Figure 1B) and during this period an arterial stiffness and blood pressure measurement was performed via an arteriograph device.

After the baseline measurements had been performed, the participants underwent a 45^{o} passive leg raising test (PLR) and a 60^{o} head-up tilt testing (HUTT) on a mechanical tilt table with safety belts (Figure 2). By means of PLR an easy, safe, and reversible fluid challenge can be given and passive HUTT induces an easily and fast reversible unloading of the central blood volume. There was a period of at least 10 minutes between the two tests, in supine position, to allow the circulation to return to baseline levels. Tilt test could prematurely be terminated in case of imminent syncope or at patients request. After 3 minutes from start of PLR and HUTT all measurements performed in supine position were repeated, as the acute phase has then passed, and the parameters of interest would have been stabilized to the new hemodynamic situation. For the continuously monitored measures, final values were obtained by averaging the 3-7 minutes period from start PLR or HUTT (periods marked in light blue in Figure 1B). At the end of the fluid challenge, after HUTT, the participants rested for at least 5 minutes in supine position.

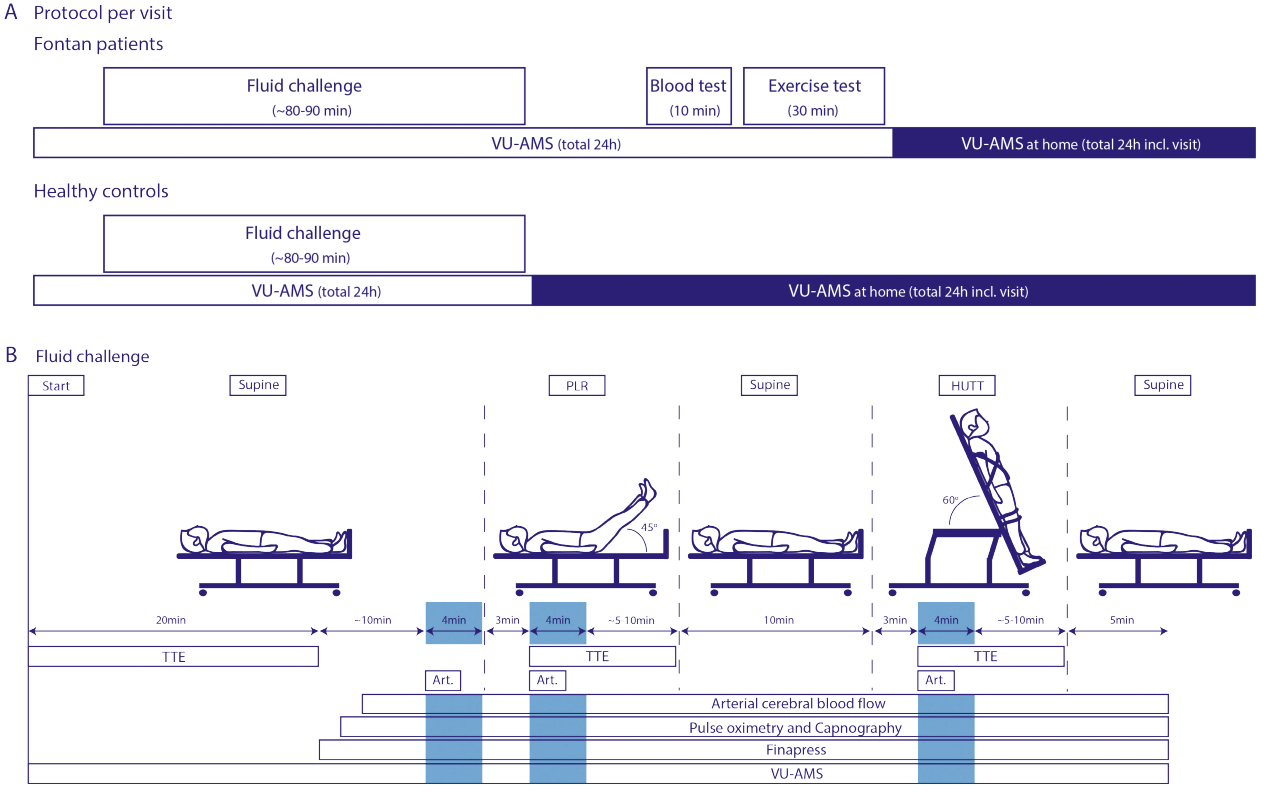

Figure 1. A: Timeline of the protocol per visit and B: Protocol of Fluid challenge. Art.= Arteriograph measurement; HUTT= Head-up tilt table; PLR= passive leg raising; TTE= Transthoracic echocardiogram; VU-AMS= VU University ambulatory monitoring system, recording electro- and impedance cardiogram.

Figure 2. Participant during HUTT

Follow-up and ACE-inhibition

Treatment with enalapril, an angiotensin converting enzyme (ACE) inhibitor, started one day after the first study visit. Treatment started with a dosage of 5mg/day and dosage was further titrated over a period of 2-3 weeks to a targeted dosage of 0.5mg/kg/day or a maximum of 20mg/day. Dosage was titrated according to blood pressure which could be measured by the general practitioners of the patients. When patients experienced side effects or when the systolic blood pressure fell more than 20%, the dosage was lowered. Renal function, measured by creatinine and urea blood levels, was checked after two weeks of treatment with the maximal tolerated dosage. This could also be checked at the general practitioner or at a local hospital near the patient's home.

After three treatment months, all procedures performed at the first study visit were repeated (Figure 1). A period of three months was chosen as studies in adult and paediatric patients had shown beneficial effects of ACE-inhibitors within 12 weeks of treatment (1-5). An overview of the follow-up of Fontan patients during the three-month enalapril treatment period is shown in Figure 3.

Echocardiography

Transthoracic echocardiograms (TTE) were performed on a Vivid S6/S60 (General Electric Healthcare, Norway) and conducted by an experienced technician or a paediatric cardiologist. Images were stored and analysed offline (using EchoPac;

version 203, GE Healthcare) by one researcher and experienced technician, supervised by a paediatric cardiologist. Echocardiography was performed in supine position and during HUTT and PLR. The supine echocardiographic assessment was more extensive than during HUTT or PLR, because for Fontan patients it was also part of a routine clinical follow-up and for healthy controls to evaluate whether they had a structurally and functionally normal heart.

Conventional echocardiography, consisting of pulse wave Doppler or in case of high velocities continuous wave Doppler, 2D echocardiography and M-mode, was performed. In addition, Tissue Doppler Imaging (TDI) and speckle tracking were performed following previously published methods (6, 7). TDI was performed to obtain myocardial velocity curves of the basal part of the systemic ventricles' lateral wall and septum. Strain images were recorded with grayscale images of the four-chamber view (longitudinal analysis) with, preferably, 60-90 frames per second. In Fontan patients, longitudinal global peak strain was conducted if 5 out of 6 segments could be recorded with acceptable curves. Furthermore, if the ventricular septum defect was larger than one segment, strain was conducted from both lateral walls. Variables extracted from the TTE and used for analysis in the sAFE-study project are summarized in Table 2. Averages of three consecutive cardiac cycles were used for analysis, if applicable.

Arteriograph

The Arteriograph (Tensiomed, Budapest, Hungary), an oscillometric device (8), was used to measure blood pressure as well as pulse wave velocity of the aorta (PWVao) and augmentation index of the aorta, both parameters of arterial stiffness. To obtain arterial stiffness measurements, the device performs two consecutive blood pressure measurements with the cuff over-inflated during the second measurement by 35-40mmHg above systolic pressure. The Arteriograph software calculates average values of each measurement and determines accuracy of the measurement with a standard deviation. A measurement is considered accurate when the standard deviation of PWVao <1.0m/s. However automatic calculation is not always possible, for example due to smaller pulse waves and movement which will distort the shape of the wave. As children exhibit smaller pulse waves and HUTT also results in smaller pulse waves, each cardiac cycle had to be analysed one by one using the software. Each measurement was visually checked by one researcher and was considered valid when a reliable value could be calculated with a standard deviation of PWVao <1.0m/s over at least two separate measurements. All measurements were performed with the cuff on the left arm. Arterial stiffness parameters derived from the Arteriograph are summarized in Table 3.

Follow-up Fontan patients

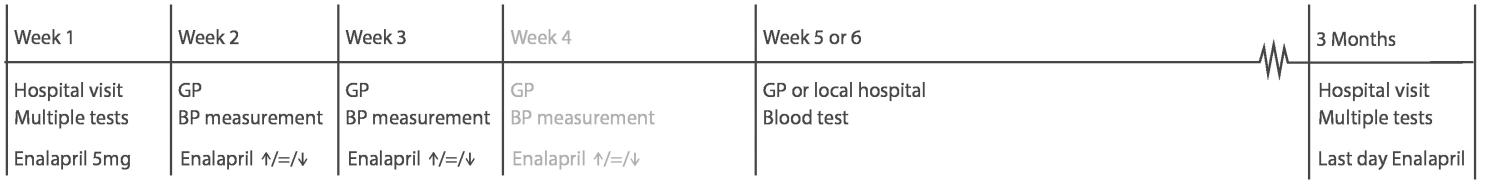

Figure 3. Timeline of Follow-up of Fontan patients. BP= Blood pressure; GP= General practitioner.

Table 2. Echocardiographic parameters

Parameter	Derived from	Parameter definition	Comment
Velocity time integral *VTI (cm)*	PW Doppler across the aortic valve	Equivalent to the area within the pulse wave doppler spectral curve	
Stroke volume index *SVI (ml/beat/m^2)*	Aortic annulus diameter and PW Doppler across the aortic valve	Multiplying the aortic cross-sectional area with VTI divided by the body surface area	
Cardiac index *CI (ml/min/m^2)*	Aortic annulus diameters, PW Doppler across the aortic valve and heart rate	Multiplying SVI with heart rate	
Longitudinal global peak strain *Global strain (%)*	Apical 4-chamber view using speckle tracking strain analysis	Peak from the global time-strain curve of the systemic ventricle	Systolic function parameter, lower value equals worse contraction
Peak myocardial velocities *Peak systolic (S'), peak early (E') and late (A') diastolic velocities (m/s)*	From Tissue Doppler Imaging, curves of the basal part of the systemic ventricles' lateral wall and septum	S' is the maximal velocity during systole, E' and A' are the maximal velocities during the early and late ventricular filling phase	A lower S' equals worse systolic function. A higher E'/A' ratio equals worse diastolic function.
Peak flow velocities *Peak early (E) and late (A) diastolic velocities (m/s)*	PW Doppler across the atrioventricular valve of the systemic ventricle	Maximal velocity during the early and late ventricular filling phase	A higher E/A ratio equals worse diastolic function
E/E' ratio	PW (E) and Tissue Doppler (E' of lateral wall) peak early diastolic velocities	Ratio of pulse wave and tissue doppler peak early diastolic velocities	A Higher E/E' ratio equals worse diastolic function
Peak hepatic flow *(m/s)*	PW Doppler hepatic vein	Maximal antegrade flow	
Inferior vena cava collapsibility index *IVC collapsibility index (%)*	Maximum and minimum diameter of IVC during sniff test, measured by M-mode	Proportional change of the IVC during sniff-test	

Table 3. Arterial stiffness parameters

Parameter	Derived from	Parameter definition	Comment
Pulse wave velocity aorta *PWVao (m/s)*	Pulse wave analysis and Jugulum-Symphisis distance	Speed of aortic blood flow: Jug-Sy distance divided by half the time between the direct systolic wave and the late/reflected systolic wave (=return time): $\frac{\text{Jug} - \text{Sy (m)}}{\text{Return time}/2\text{ (s)}}$	Higher value equals a stiffer vessel
Aortic augmentation index *AIXao (%)*	Pulse wave analysis	Blood pulse wave reflection: Difference between the late/reflected (P2) and early (P1) systolic wave pressure, expressed as a percentage of the pulse pressure (PP): $\frac{\text{P2} - \text{P1}}{\text{PP}} \text{ X } 100$	Higher value equals a stiffer vessel; influenced by heart rate

Arterial cerebral blood flow

Transcranial Doppler sonography was performed to assess the mean velocity blood flow of both cerebri media arteries. Sonography was assessed by two 2MHz probes which were attached to an adjusted Marc 500 headframe (Spencer Technology, America; Figure 4) and Doppler signals processed by a non-imaging Doppler-Box with DWL Doppler system and QL software version 3.3 (Compumedics Germany, supplied by VCM medical, Netherlands). Although sonography of both arteries was assessed, the artery with the highest mean velocity was used for analysis (Table 4). Sonography of cerebral arteries is challenging and depends on the echo window of the temporal bone. Due to insufficient echo windows, cerebral blood flow measurements could only be assessed in 19 Fontan patients and 27 controls in the sAFE study.

Pulse oximetry and Capnography

Pulse oximetry was performed with a Nihon Kohden (Japan) finger clip pulse oximeter to measure blood oxygen saturation. Furthermore, capnography was performed by a capONE mainstream CO_2 sensor with a nasal/oral adapter (Figure 4) to measure end-tidal CO_2. Definitions of both parameters are shown in Table 4.

Table 4. Arterial cerebral blood flow measurement, pulse oximetry and capnography

Parameter	Derived from	Parameter definition	Comment
Mean arterial velocity of the artery cerebri media *MAV art. cerebri media (cm/s)*	Transcranial Doppler sonography	Mean velocity of the artery cerebri media.	The artery with the highest mean flow was used for analysis
Oxygen saturation *SpO_2 (%)*	Pulse oximetry	The fraction of oxygen-saturated haemoglobin relative to total haemoglobin in the blood.	
End-tidal CO_2 *$EtCO_2$(mmHg)*	Capnography	The level of carbon dioxide that is released at the end of an exhaled breath.	

Finapress

During the fluid challenge blood pressure was continuously monitored by finger plethysmography with use of a Finometer (Finapress, The Netherlands, Figure 4). Monitoring of blood pressure during tilt test is essential to recognize possible imminent syncope and to abort the tilt test in time before real syncope occurs. As blood pressure is accurately measured by a the arteriograph at baseline, PLR, and HUTT we used the data of blood pressure measurements of the arteriograph for analysis within the sAFE study. By use of Modelflow, the data from the Finometer can be used to calculate stroke volume, cardiac output, and peripheral resistance, among other things. The Modelflow method is, however, a good method for adult patients and has not yet been validated in children. Furthermore, preliminary analysis revealed that the Modelflow method was also not suitable to analyse the altered circulation in Fontan patients. Therefore, data from the Finapress has not been used in the analysis and will not be discussed further.

VU-AMS

The VU Ambulatory Monitoring System (VU-AMS; VU University, Amsterdam, The Netherlands, www.vu-ams.nl) was used to conduct ICG and ECG recordings to assess different cardiac autonomic nervous system activity parameters and respiration (9). Three pregelled Ag/AgCL (Kendal H124SG) spot electrodes on the chest were used to derive a one lead ECG (Figure 5). Thoracic ICG was conducted by introducing a small alternating current (50kHz, 350μA) through the thorax by use of four spot electrodes (same as used for the one lead ECG), two electrodes on the thorax, just above and below the sternum, and the two current electrodes on the back of the thorax, place 3 cm above and below the electrodes from the front of the thorax (Figure 5). The VU-AMS records ECG and ICG by using a sample rate of respectively 1000 and 250Hz.

In this study the 5fs version of the VU-AMS version was used. Furthermore, the VU Data Analysis and Management Software (VU-DAMS; VU-University) was used to analyse the date offline. Ectopic beats and artefacts were removed in the VU-DAMS program after an automated scoring of R-peaks and artefact detection by the software and a final visual check of the ECG. A total of six Fontan patients were excluded for analysis due to an atrial ectopy or a nodal rhythm. In addition, one other patient was also excluded from analysis due to a pacemaker.

Variables extracted from the ECG and ICG recordings and used for analysis in the sAFE-study project are summarized in Table 5.

Figure 4. Participant with headframe, nasal/oral adapter and Finapress (around wrist and middle finger)

Figure 5. Participant with the VU-AMS electrodes on the thorax.

Blood test

At baseline and after three treatment months plasma N-terminal pro brain natriuretic peptide (NT-pro BNP) levels were assessed to evaluate the effect of enalapril treatment. NT-pro BNP is a non-active prohormone that is released in response to changes in pressure in the heart and can be related to heart failure. Higher NT-pro BNP levels are associated with heart failure and worse physical function.

As ACE inhibition may affect renal function, renal function was assessed at baseline, after two weeks of treatment with the maximal tolerated dosage and at the end of the study after three months of treatment. Renal function was measured by assessing plasma creatinine and urea levels.

Table 5. Parameters derived from VU-AMS

Parameter	Derived from	Parameter definition	Comment
Respiration Sinus Arrhythmia *RSA (ms)*	ECG & ICG	Difference between the longest inter-beat interval during exhalation and the shortest inter-beat interval during inhalation	Measure of cardiac parasympathetic (PNS) control. A higher value equals higher PNS activity
Root mean square of successive differences *RMSSD (ms)*	ECG	Root mean square of successive differences	Measure of cardiac parasympathetic control. A higher value equals higher PNS activity
Standard deviation of the inter-beat intervals *SDNN (ms)*	ECG	Standard deviation of the inter-beat intervals	Measure of cardiac parasympathetic control. A higher value equals higher PNS activity
Low frequency power spectral values *LF (ms^2)*	ECG	Absolute power of the low-frequency band (0.04-0.15Hz)	Both parasympathetic and sympathetic activity contributes to LF power.
High frequency power spectral values *HF (ms^2)*	ECG	Absolute power of the high-frequency band (0.15-0.4Hz)	Parasympathetic activity primarily contributes to HF power.
Low frequency/high frequency ratio *LF:HF*	ECG	Ratio of LF to HF power	Measure of sympathicovagal balance, however, controversial as LF is not a pure measure of sympathetic activity
Pre-ejection period *PEP (ms)*	ECG & ICG	Time difference between the start of electrical depolarization (i.e., Q-wave onset on ECG) and start of left ventricular outflow (i.e., B-point in the ICG signal)	Measure of cardiac sympathetic control. A lower value equals a higher sympathetic activity
Respiration rate *RR (breaths/min)*	ICG	Number of breaths per minute	

Cardiopulmonary exercise test

Cardiopulmonary exercise tests were performed in upright position on a bicycle ergometer (Jaeger ER 900; Viasys Healthcare, Höchberg, Germany) with breath-by-breath analysis using a flowmeter (Triple V volume transducer) and computerized gas analyser (Jaeger Oxycon Champion, Viasys Healthcare or Carefusion Vyntus, Vyaire Medical) (Figure 6). Breath-by-breath minute ventilation (VE), oxygen uptake (VO_2), carbon dioxide production (VCO_2) and respiratory exchange ratio (RER,

defined as VCO_2/VO_2 ratio) were conducted per 10 seconds. Furthermore, heart rate was continuously monitored through a twelve lead ECG and blood pressure was measured every two minutes. Starting wattage and workload increment per minute were determined by the physician and by the age of the patient. For Fontan patients who underwent the exercise test at baseline and after three months of treatment, the same starting wattage and workload increment per minute was used for both tests. During the test, the patients had to maintain a pedalling rate between 60-65 revolutions per minute. Patients were encouraged by the technician, physician, and researcher to exercise until exhaustion. The test was ended by the patient in case of discomfort or by the supervising physician in case of ECG changes, an excessive breathing pattern or otherwise. After cessation of the test, the patient was instructed to pedal at <40 revolutions per minute with no resistance for at least two minutes. The ECG was detached when the heart rate had returned to resting values.

Variables extracted from the cardiopulmonary exercise test are summarized in Table 6. A test was considered maximally performed when RER was ≥1.0. Maximally exercise parameters were only determined in patients who had an RER ≥1.0, submaximal parameters were assessed in all patients.

Besides absolute values, the percentage of predicted values adjusted for age and sex were calculated, where applicable, using previous published methods (10-12), except for peak oxygen uptake ($VO_{2\,peak}$) which was adjusted for age, sex, weight and height (13) and oxygen pulse for which we used the data of Ten Harkel et al. (10).

Table 6. Parameters derived from cardiopulmonary exercise test

Parameter	Derived from	Parameter definition	Comment
Peak respiratory exchange ratio *RER_{peak}*	Breath-by-breath analyser	Respiratory exchange ratio at peak exercise, calculated by dividing carbon dioxide production by oxygen uptake at peak exercise (VCO_2/VO_2).	An RER of 1.0 is the aerobic threshold. A test was considered maximally performed when RER was ≥1.0.
Maximal exercise parameters			
Peak work rate *WR_{peak} (watt or watt/kg)*	Power meter	Highest work rate achieved and finished (1 minute completed).	
Peak heart rate *HR_{peak} (bpm)*	ECG	Highest heart rate at peak exercise	Measure of chronotropic competence
Heart rate reserve *HR reserve (bpm)*	ECG	Difference between peak heart rate and resting heart rate (measured from baseline ECG laying on the bench before exercise test)	Measure of chronotropic competence
Heart rate recovery at 1 min in % *HR01 percentage (%)*	ECG	Percentage heart rate recovery at 1 minute after exercise in relation to heart rate reserve: $\frac{\text{HR peak exercise} - \text{HR1min. after exercise}}{\text{HR reserve}} x100$	
Peak oxygen uptake *VO_{2peak} (L/min or ml/kg/min)*	Breath-by-breath analyser	Highest measured oxygen consumption at peak exercise	Measure of aerobic fitness
Peak O_2 pulse *(ml/beat)*	Breath-by-breath analyser and ECG	Peak oxygen uptake per heartbeat.	Has been used as a correlation of stroke volume

Table 6. Parameters derived from cardiopulmonary exercise test (continued)

Parameter	Derived from	Parameter definition	Comment
Submaximal exercise parameters			
Respiratory minute to CO_2 production slope *VE/VCO_2 slope*	Breath-by-breath analyser	Slope of the linear regression of ventilatory efficiency (VE) and CO_2 production (VCO2) during the entire period of the test.	Measure of anaerobic fitness A higher slope reflects poor ventilatory efficiency
Oxygen uptake efficiency slope *OUES*	Breath-by-breath analyser	Linear least squares regression of the oxygen uptake (VO_2) on the common logarithm of the ventilatory efficiency (VE) by the equation: VO_2 = a log (VE) + b, where the constant a is the regression coefficient.	Measure of anaerobic fitness
Oxygen uptake efficiency plateau *OUEP*	Breath-by-breath analyser	The 90-sec average of the highest consecutive oxygen uptake efficiency (OUE) values (OUE= ventilatory efficiency divided by oxygen uptake, VE/VO_2)	Measure of anaerobic fitness

Figure 6. Participant performing a cardiopulmonary exercise test

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