

## Exercise limitation in patients with Fontan circulation: a review

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The aim of the current literature study was to perform a literature review of the factors contributing to exercise limitation and physiological response to exercise in patients with Fontan circulation. In patients with Fontan circulation, peak oxygen uptake ranged from about 14.4 to 32.3 ml/min/kg, and showed a slowed acceleration in the kinetics of oxygen uptake at the onset of exercise. Peak heart rate during exercise was decreased to an average of  $153 \pm 10$  bpm and arterial oxygen saturation was also decreased at peak exercise, with an average of  $89.5 \pm 1.94\%$ . Cardiac output was subnormal, owing to reduced stroke volume, heart rate response and affected pulmonary venous return. Ventilatory anaerobic threshold was below normal values. Moreover, the ventilatory equivalent for carbon dioxide was found to be higher. Patients with Fontan circulation possess a unique physiological response to exercise. Although there is a wide range in exercise capacity among patients, all patients have

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### Introduction

Congenital heart defects, with an incidence of 6–8 per 1000 live births, comprise a broad spectrum of disorders. Single-ventricle hearts include a heterogeneous group of defects that are not suitable for a two-ventricle repair. In 1971 Fontan and Baudet [1] described a surgical procedure to palliate such hearts by separating the systemic and pulmonary venous return. This was introduced to obtain normal oxygenation and to avoid volume overloading. In this so-called 'Fontan circulation', the systemic venous return is connected to the pulmonary arteries without the interposition of an adequate ventricle, and all shunts on the venous, atrial, ventricular and arterial level are interrupted [2].

Exercise capacity provides information on the functioning of the cardiovascular, ventilatory and muscular system of a subject [3,4], and also gives insights into the functional capacity of that subject [5]. Moreover, it is an important predictor of outcome and survival in patients with cardiovascular disease [6], as well as in healthy subjects [6,7]. Therefore, measurement of exercise capacity has become widespread in adult [8] and paediatric cardiology practice [9]. Several professional organisations have published guidelines for the performance and

interpretation of maximal exercise tests in both adults [10–12] and children [13].

Numerous studies have been undertaken with the aim at studying exercise capacity in children, adolescents and adults with Fontan circulation. In most of them, data from maximal exercise tests were reported. The purpose of the present literature study was to perform a literature review of the factors contributing to exercise limitation and physiological response to exercise in patients with Fontan circulation.

### Search strategy

The literature was selected from Medline, Embase and Sportdiscus databases covering the years 1966–2005. Search terms were 'physical fitness', 'exercise testing', 'exercise', 'exercise capacity', 'exercise tolerance', 'Fontan', and 'univentricular'. References of the selected publications were tracked to find additional publications on this subject. Selected publications had to include a description of an exercise stress test with one or more exercise parameters, such as peak oxygen uptake ( $\text{VO}_2$ ), maximal  $\text{VO}_2$ , or determination of the ventilatory anaerobic threshold (VAT). Also the publications in

which direct measured values of peak  $\text{VO}_2$  were reported, including a full description of the methods and patient characteristics, were included in this investigation.

### Experimental findings

Thirty-one studies were identified investigating the exercise capacity of 694 patients with Fontan circulation. As some studies are from the same laboratory, it is reasonable to assume that in those studies several patients are included more than once.

During exercise, several parameters can be measured. In addition to peak workload and heart rate, gas exchange can be measured. In this review, we will address the exercise response on the following parameters: peak workload, maximal  $\text{VO}_2$  and  $\text{VO}_2$  kinetics, heart rate, arterial oxygen saturation ( $\text{SaO}_2$ ), cardiac output and stroke volume, blood pressure, respiratory exchange ratio, VAT and ventilatory responses.

### Peak workload

Peak workload is the maximal workload a subject can attain during an exercise test. The results of 11 studies are shown in Table 1 [14–43]. Driscoll *et al.* [17] reported levels of peak workload for 81 patients with single ventricle prior to, and 27 patients after, the Fontan

operation. They found that peak workload preoperatively was  $25 \pm 16.5\%$  of the predicted value, increasing significantly postoperatively to  $37 \pm 17.7\%$ . Other studies reported peak workload values in Fontan patients ranging from  $47 \pm 21\%$  [18] to  $66 \pm 14\%$  of the predicted value [34]. All studies found a reduced peak workload; however, the magnitude of the impairment was heterogeneous among the different studies.

### Peak oxygen uptake

Peak  $\text{VO}_2$  is the highest oxygen consumption a patient can attain for a specific type of exercise [44], and is widely recognised as the best single indicator of cardiopulmonary function in children and adults [45]. It has been shown that also 5–6-year-old children are able to perform maximal exercise tests on a bicycle ergometer or treadmill [46].

Twenty-nine studies reported peak  $\text{VO}_2$  values. As can be appreciated from Table 1 [14–43], peak  $\text{VO}_2$  is reduced after Fontan operation and ranged from about 14.4 to 32.3 ml/kg/min. Driscoll *et al.* [17] reported levels of peak  $\text{VO}_2$  for 81 patients with single ventricle prior to and 27 patients after the Fontan operation. Peak  $\text{VO}_2$  increased from 20.5 ml/kg/min preoperatively to 24.3 ml/kg/min postoperatively. A reduced peak  $\text{VO}_2$  in

**Table 1 Peak workload, peak oxygen uptake ( $\text{VO}_2$ ), peak heart rate (HR), and arterial oxygen saturation ( $\text{SaO}_2$ ) during maximal exercise in patients with Fontan circulation**

Study	Age at test (years)	No. patients	Peak workload (W)	Peak $\text{VO}_2$ (ml/kg/min)	Peak HR (bpm)	$\text{SaO}_2$ (%)
Brassard <i>et al.</i> [14]	16 ± 5	7	103 ± 42	28.0 ± 7.0	156 ± 27	91 ± 4
Chua <i>et al.</i> [15]	30.5 ± 2.3	8		21.0 ± 1.9	133.4 ± 10.0	90.5 ± 2.1
Cortes <i>et al.</i> [16]	6.9–24.9	16			156 ± 16	
Driscoll <i>et al.</i> [17]	14.6 ± 7	27	25 ± 16.5% of predicted	24.3	81% of predicted	91
Driscoll <i>et al.</i> [18]	6–36	9	47 ± 21% of predicted	56 ± 15% of predicted		
Durongpisitkul <i>et al.</i> [19]	5–41	59		60.5 ± 16.9% of predicted	148 ± 24.33	89.5 ± 4.2
Fredriksen <i>et al.</i> [20]	18–45	52		15.9 ± 4.0	139 ± 25	87 ± 5
Garcia <i>et al.</i> [21]	14.5 ± 5.2	11	79 ± 34.9	23.5 ± 5.3	161.8 ± 13.2	89.3 ± 6.2
Grant <i>et al.</i> [22]	6–25	13		23.3 ± 6.1	163 ± 15	87 ± 9
Harrison <i>et al.</i> [23]	26.6 ± 6.6	30		14.8 ± 4.5		
Inai <i>et al.</i> [24]	21 ± 7	50		21 ± 6	151 ± 21	93 ± 2
Iserin <i>et al.</i> [25]	29.4 ± 1.5	8		21.0 ± 1.9	133.4 ± 10.0	90.5 ± 2.1
Joshi <i>et al.</i> [26]	7.3 ± 1.5	21		25.9 ± 5.4	146 ± 15	90.7 ± 5.7
Mahle <i>et al.</i> [27]	9.2 ± 2.1	46		32.3 ± 8.9	155.9 ± 21.0	92.2 ± 3.9
Minamisawa <i>et al.</i> [28]	19 ± 4	11		76.1 ± 21.1% of predicted		
Miyairi <i>et al.</i> [29]	9.1–16.5	8		24.7 ± 5.0	166 ± 12	
Mocellin and Gildein [30]	8.8	5		19.8 ± 3.4	163 ± 11	
Nir <i>et al.</i> [31]	3.8–39	25		28.5 ± 4.1		
Ohuchi <i>et al.</i> [32]	17 ± 3	13		23.9 ± 9.2	138.3 ± 29.0	90.7 ± 4.3
Ohuchi <i>et al.</i> [33]	14 ± 4	33		55.6 ± 18.4% of predicted	71.4 ± 15.2% of predicted	
Ohuchi <i>et al.</i> [34]	12 ± 4	33	66 ± 14% of predicted	24.9 ± 1.2	162 ± 4	
Opocher <i>et al.</i> [35]	8.7 ± 0.6	10		23.5 ± 5.4	164 ± 17	
Rhodes [36]	17.4 ± 5.2	11	59.6 ± 10.0% of predicted	25 ± 4	161 ± 20	
Stromvall-Larsson <i>et al.</i> [37,38]	18.3–26.4	15	95	55 ± 9% of predicted	84 ± 11% of predicted	
Stromvall-Larsson <i>et al.</i> [39]	11.6–54.2	18	105	27 ± 5	159 ± 20	
Troutman <i>et al.</i> [40]	12.2 ± 2.4	16	78 ± 32	24.3	156	89.0 ± 5.1
Weipert <i>et al.</i> [41]	11–29	15		59.8 ± 17.5% of predicted	97.7 ± 5.7% of predicted	
Zajac <i>et al.</i> [42]	5.7–17	14	80.8 ± 45.7	22.7	147	86
Zellers <i>et al.</i> [43]	7–35	20	66 ± 18% of predicted	25.3	151.7	
				57% of predicted	164 ± 16	88.9 ± 4.2
				24.7 ± 1.6	152 ± 3.9	
				61.6 ± 6.3% of predicted	84.4 ± 3.9% of predicted	
				14.4 ± 6.1	142.2 ± 24.8	87.1 ± 4.3
				27 ± 6	81 ± 10% of predicted	90 ± 3
				59 ± 15% of predicted		

patients after the Fontan operation was also found by Joshi *et al.* [26]. They found an average peak  $\text{VO}_2$  of 25.9 ml/kg/min in patients with hypoplastic left-heart syndrome, an average peak  $\text{VO}_2$  of 21.6 ml/kg/min in patients with systemic morphological right ventricle, and an average peak  $\text{VO}_2$  of 20.7 ml/kg/min in patients with morphological left systemic ventricle.

In the study of Nir *et al.* [31] exercise tests were performed in 25 patients after an average of 2.2 years and of 5.9 years of follow-up. Peak  $\text{VO}_2$  was reduced during both tests, with 24 ml/kg/min in the first and 25 ml/kg/min in the second assessment. The maximal  $\text{VO}_2$  was related neither to age at surgery nor to age at which the first test was performed. A possible reason for the lower peak  $\text{VO}_2$  may be the inability to increase cardiac output [23]. Another reason could be a reduced physical activity level in the Fontan patients compared with the reference population [20]. Age at surgery, regardless of type of intervention, was the most important factor in determining peak  $\text{VO}_2$ . The younger the patients at the time of surgery, the higher their peak  $\text{VO}_2$  at late follow-up [20,43]. Nir *et al.* [31], however, reported no significant relationship between age at surgery and peak  $\text{VO}_2$ .

#### Oxygen uptake kinetics

$\text{VO}_2$  kinetics indicates the relative aerobic and anaerobic metabolic contributions to a given change in exercise intensity, and take into account pulmonary limitations [45]. Two studies investigated  $\text{VO}_2$  kinetics [30,47]. Mocellin and Gildein [30] found that patients with Fontan circulation, compared to children after corrective surgery for tetralogy of Fallot and transposition of the great arteries, showed the most marked slowing of half-time values for  $\text{VO}_2$  (35.4 s compared to 31.8 s for children with transposition of the great arteries, 30.6 s for children with tetralogy of Fallot, and 22 s for healthy controls). Mertens *et al.* [47] found an increased oxygen deficit at the onset of a constant workload test on the treadmill, indicating decreased  $\text{VO}_2$  kinetics and suggesting a slowed cardiorespiratory adaptation to exercise. This decreased  $\text{VO}_2$  kinetics was associated with a blunted heart rate response during the early phase of exercise. During the first stages of exercise, the rapid increase in oxygen consumption is a function of a rapid increase in cardiac output. Heart rate acceleration and, to a lesser extent, the increase in stroke volume are major determinants for the cardiac output response at the onset of exercise [48]. Decreased  $\text{VO}_2$  kinetics in patients with Fontan circulation can be partially explained by a blunted heart rate response during the very early stages of exercise, since Fontan patients cannot accelerate their heart rate as quickly as normal subjects do [47]. The impaired heart rate response could partly be due to the previous extensive atrial surgery at the time when the Fontan circuit was created, which could have potentially damaged the sinus node [47,37]. An alternative explanation is

that in Fontan patients (especially those with a total cavopulmonary connection), the increased venous return caused by activating the muscle pump is directed immediately to the pulmonary circulation, bypassing the right atrium [47]. In normal patients, stretching of the right atrium due to increased preload is an important contributing factor to heart rate acceleration during exercise. In patients with Fontan circulation either chronic atrial stretching (right atrial to pulmonary circulation) or the direct diversion of blood flow to the pulmonary circulation (total cavopulmonary connection) results in decreased heart rate acceleration [47]. Finally, the reduced heart rate response could reflect a blunted sympathetic response to exercise [47,37]. Also a blunted increase in stroke volume during the onset of exercise could contribute to the decreased cardiac output response during the onset of exercise [47]. Fontan patients might have a reduced capacity to increase pulmonary blood flow during exercise resulting in a reduced increase in preload to the single ventricle. The observed slower increase in  $\text{VO}_2$  kinetics in the study of Mertens *et al.* [47] between 10 and 60 s of exercise, and not during 20 and 60 s, compared to control subjects, suggests that the first phase or cardiodynamic phase of the response of  $\text{VO}_2$  at the onset of exercise is impaired. The cardiodynamic phase is mainly determined by an increase in cardiac output rather than a change in the arteriovenous oxygen difference [48].

Since peak  $\text{VO}_2$  and VAT are reduced in patients with Fontan circulation, the same absolute exercise intensity reflects a relatively higher intensity of exercise in patients with Fontan circulation, compared to normal controls. This will also slow  $\text{VO}_2$  kinetics, which also contributes to a higher oxygen deficit at the onset of exercise [47].

#### Heart rate

Twenty-five studies reported peak heart rate values with significantly lower peak heart rates compared to healthy peers (Table 1) [14–43]. The average peak heart rate recorded during the exercise tests was  $153 \pm 10$  bpm. Moreover, Driscoll *et al.* [17] found a reduced peak heart rate (81% of predicted) along with an increased resting heart rate ( $107 \pm 18\%$  of predicted). An increased resting heart rate in patients with Fontan circulation was also observed in other studies [16,49]. Both increased resting and diminished peak heart rate values result in reduced heart rate reserve (difference between peak and resting heart rate).

#### Arterial oxygen saturation

Theoretically,  $\text{SaO}_2$  should be normalised after the Fontan operation, but  $\text{SaO}_2$  is slightly lower than normal at rest and decreases even further with exercise. As can be seen in Table 1 [14–43],  $\text{SaO}_2$  was reported in 17 studies and was on average  $89.5 \pm 1.94\%$  at peak exercise. The reduced  $\text{SaO}_2$  could be caused by one or more factors,

including persistent intrapulmonary right-to-left shunt, coronary sinus blood return to the pulmonary venous atrium, and persistent intracardiac right-to-left shunts [50]. Most patients after Fontan surgery show a decrease in the upper to lower lobe pulmonary blood flow perfusion rate. Matsushita *et al.* [51] studied 12 postoperative patients and noted an abnormal distribution of pulmonary blood flow with increased flow to the upper lobes compared to normal. They also observed increased pulmonary vascular resistance, which they attributed to the relatively increased blood flow to the upper lobes. These authors suggested that this abnormal perfusion pattern may provide a ventilation–perfusion mismatch, explaining the reduced SaO<sub>2</sub> after the Fontan operation. Grant *et al.* [22] reported increased physiological dead space and ventilation–perfusion mismatch consistent with maldistribution of pulmonary blood flow. The fact that intrapulmonary shunting can increase over time postoperatively was suggested by Nir *et al.* [31], who reported lower SaO<sub>2</sub> at peak exercise during exercise tests performed an average of 5.9 years compared to those performed an average of 2.2 years postoperatively. In the absence of a pronounced intracardiac shunt, it has been suggested that drainage of the coronary sinus to the pulmonary venous atrium may explain some of the desaturation [31].

#### Cardiac output and stroke volume

Four studies evaluated cardiac output at rest and during exercise in patients with Fontan circulation [16,17,19,38]. They reported resting cardiac outputs ranging from 60 to 70% of normal. Cortes *et al.* [16], however, found that the cardiac index (cardiac output per square metre of body surface area) at rest was similar in patients with Fontan circulation compared to a control group. During exercise, cardiac output increased with respect to resting values; however, cardiac output rapidly reached a plateau during exercise. When compared to normal subjects, the cardiac output response to exercise in Fontan patients was subnormal [17].

The cause of the reduced cardiac output response to exercise is multifactorial. As reported by some investigators, the stroke volume and heart rate response to exercise is subnormal. This could contribute to a reduced increase in cardiac output during exercise [16,47,52]. It may also be secondary to a limiting factor outside the heart; for instance, in the Fontan circulation the pulmonary venous return is significantly affected during tachycardia [16]. Patients exhibit an increase in the resistance to venous return, which includes the series arrangement of the systemic and pulmonary vascular beds [53]. Hence, even if the systemic resistance decreases dramatically during exercise, the resistance to venous return is still quite elevated because of the series arrangement of the pulmonary vascular bed. Also systemic resistance is elevated owing to vasoconstriction of peripheral arterioles

caused by baroreflex control. This phenomenon contributes further to a reduced cardiac output [53].

Several authors have reported a reduced stroke volume response to exercise [16,17,49]. There is a subnormal response of stroke volume at submaximal exercise and failure to maintain increased stroke volume with increasing exercise, resulting in decreased maximal exercise capacity [23]. The lower increase in stroke volume with exercise and the significant decline at the point of maximal effort can be explained by a limited diastolic return to the systemic ventricle [16], a right atrial to right ventricular type of Fontan connection, a poor ventricular function, and a high preoperative mean pulmonary artery pressure [49].

Thus during exercise, VO<sub>2</sub> relative to cardiac output is significantly higher in Fontan patients compared to healthy controls [38], indicating impeded oxygen delivery to the working muscle [54].

#### Blood pressure response

Four studies reported the blood pressure response in Fontan patients during exercise [20,38,43,54]. In Fontan patients, systolic blood pressure at rest was normal (98% of predicted), and it increased appropriately with exercise (87% of predicted) [43]. Similarly, diastolic blood pressure was within normal limits at rest and during exercise (101% of predicted at rest, 100% of predicted during exercise) [43]. Fredriksen *et al.* [20] found maximum systolic blood pressure to be 150 mmHg and diastolic blood pressure 77 mmHg. Up to submaximal levels of exercise, arterial blood pressure is relatively well maintained, partly because of increased systemic arterial resistance [38]. Peak levels, however, are usually lower than in healthy controls because of an impaired increase in cardiac output at peak exercise [54].

#### Respiratory exchange ratio

The respiratory exchange ratio is a useful parameter, both as a marker of effort and as an indicator of substrate utilisation during exercise [45]. The respiratory exchange ratio is the ratio of carbon dioxide expired to the VO<sub>2</sub> per unit time and reflects the tissue level exchange of oxygen and carbon dioxide. In 15 studies, peak respiratory exchange ratio values were reported and were  $1.06 \pm 0.05$  on average, which is quite similar to healthy subjects. However, these peak respiratory exchange ratios are found at a significantly lower peak VO<sub>2</sub> compared with controls.

#### Ventilatory anaerobic threshold

VAT has traditionally been considered to be the point at which oxygen supply no longer meets the oxygen demands of the working muscle. The increasing contribution from anaerobic metabolism is reflected by a rapidly rising blood lactate level [45]. Six studies

**Table 2 Ventilatory responses at peak exercise in Fontan patients**

Study	Age (years)	No. patients	Peak RER	VAT (ml/kg/min)	VE (l/min)	VE/MVV ratio	VE/V <sub>O</sub> <sub>2</sub> ratio	VE/VCO <sub>2</sub> ratio
Brassard <i>et al.</i> [14]	16 ± 5	7	1.14 ± 0.08		61.5 ± 18.4		46.1 ± 8.3 124% of predicted	40.5 ± 7.5 130% of predicted
Chua <i>et al.</i> [15]	30.5 ± 2.3	8	1.16 ± 0.04			0.6 ± 0.19	114% of predicted	135% of predicted
Driscoll <i>et al.</i> [17]	14.6 ± 7	27						
Driscoll <i>et al.</i> [18]	6–36	9						
Durongpisitkul <i>et al.</i> [19]	5–41	59	1.05 ± 0.13		38.4 ± 17.5	0.52 ± 0.18	44 ± 9	
Garcia <i>et al.</i> [21]	14.5 ± 5.2	11	1.08 ± 0.08			0.53 ± 0.21	37.1 ± 6.8	
Grant <i>et al.</i> [22]	6–25	13	1.02 ± 0.16		39.8 ± 9.7	0.55	137% of predicted	135% of predicted
Harrison <i>et al.</i> [23]	26.6 ± 6.6	30		11.2 ± 2.9	57 ± 18			
Inai <i>et al.</i> [24]	21 ± 6	50	1.14 ± 0.06	18 ± 5				
Iserin <i>et al.</i> [25]	29.4 ± 1.5	8	1.16 ± 0.04			0.95 ± 0.16		136% of predicted
Joshi <i>et al.</i> [26]	7.3 ± 1.5	21	1.03 ± 0.06		78.7% of predicted			
Mable <i>et al.</i> [27]	9.2 ± 2.1	46	1.05 ± 0.10		44.4 ± 7.6			
Minamisawa <i>et al.</i> [28]	19 ± 4	11	1.10 ± 0.07		38.6 ± 15.0	0.46 ± 0.14	40.9 ± 11.5	
Nir <i>et al.</i> [31]	3.8–39	25			71% of predicted	88% of predicted		127% of predicted
Ohuchi <i>et al.</i> [32]	17 ± 3	13		17 ± 3		0.66		49 ± 9
Ohuchi <i>et al.</i> [34]	12 ± 4	33		68 ± 11% of predicted				
Rhodes [36]	17.4 ± 5.2	11			81.5 ± 30.7% of control		131.0 ± 34.3% of control	
Stromvall-Larsson <i>et al.</i> [37]	18.3	15	1.04		62.5		41.9	
Stromvall-Larsson <i>et al.</i> [39]	11.6–54.2	18	1.10		72.8		47.8	
Troutman <i>et al.</i> [40]	12.2 ± 2.4	16		52% of predicted				
Weipert <i>et al.</i> [41]	11–29	15		72% of predicted				
Zajac <i>et al.</i> [42]	5.7–17	14	1.02	36% of predicted	25.8 ± 10.6		67.9	66.15
Reybrouck <i>et al.</i> [55]	11.6 ± 4	79	98% of predicted	68 ± 9% of predicted	56.7% of predicted		165.6% of predicted	162% of predicted

RER, respiratory exchange ratio; VAT, ventilatory anaerobic threshold; VE, ventilation; VE/MVV, ratio of minute ventilation to maximal voluntary ventilation; VE/VCO<sub>2</sub>, ventilatory equivalent for carbon dioxide; VE/V<sub>O</sub><sub>2</sub>, ventilatory equivalent for oxygen.

reported VAT results and found reduced VAT values (52–68% of predicted). However, VAT is difficult to determine in cardiac patients with low peak  $\text{VO}_2$  and is not detectable in up to 10% of children with congenital heart disease [45].

### Ventilatory responses

Several studies have investigated the ventilatory responses to exercise. Seven studies reported the breathing reserve at peak exercise and found an average breathing reserve of 0.61 (Table 2) [14,15,17–19,21–28,31,32,34,36,37,39–42,55], indicating that pulmonary function limitation is not a major contributing factor to exercise intolerance in patients with Fontan circulation. Driscoll *et al.* [17] found a significantly lower breathing reserve in Fontan patients compared to normal subjects ( $53 \pm 17.2$  versus  $64 \pm 17\%$ ). On the other hand, Grant *et al.* [22] reported a non-significant difference in breathing reserve between Fontan patients and healthy controls ( $55 \pm 21$  versus  $50 \pm 13\%$ ). Moreover, a recent report found a high correlation between pulmonary function and exercise capacity in patients with Fontan circulation [56], indicating that reduced pulmonary function might limit exercise capacity in this patient group.

However, patients over-ventilate at rest and during exercise. This is manifested by an elevated ventilatory equivalent for oxygen ( $\text{VE}/\text{VO}_2$  ratio) at rest and at peak exercise (Table 2). Eleven studies reported the  $\text{VE}/\text{VO}_2$  ratio with a mean ratio of 134% of the predicted value. The ventilatory equivalent for carbon dioxide ( $\text{VE}/\text{VCO}_2$  ratio) showed the same trend (137% of predicted). A different breathing pattern might also contribute to increased  $\text{VE}/\text{VO}_2$  and  $\text{VE}/\text{VCO}_2$  ratios. In patients with a total cavopulmonary connection, both Driscoll *et al.* [17] and Zellers *et al.* [43] found a significant increase in the respiratory rate early after exercise with a lower tidal volume. The increased  $\text{VE}/\text{VO}_2$  and  $\text{VE}/\text{VCO}_2$  ratios reflect the small but persistent right-to-left shunt, and the increased physiological dead space to tidal volume ratio that results from ventilation–perfusion mismatch [52]. Furthermore, ventilation is stimulated by the presence of hypoxia, but perhaps more importantly, ventilation must be increased to maintain acid–base balance by elimination of carbon dioxide [43,57].

### Hypoactivity

A hypoactive lifestyle may contribute to reduced exercise capacity. Several small studies have investigated the effects of physical training in children and adolescents with Fontan circulation [14,28,35,58]. These studies indicate that exercise training in this population is safe. Moreover, it was shown that, when general exercise prescription guidelines are taken into account (exercising two or more times a week, at 60–80% of peak heart rate, 20–45 min of aerobic activities, i.e. cycling, walking, etc.), exercise capacity of patients with Fontan circulation can

be improved [28,35]. After 2–3 months of training, however, exercise capacity, even though improved, was still reduced compared to healthy control subjects. Results from another study indicate that exercise training might be beneficial. These authors found a strong significant correlation between muscle strength and peak  $\text{VO}_2$  [14], suggesting an important role for the skeletal muscle in the exercise limitation of patients with Fontan circulation. A rigorous trial with a larger number of subjects, including a control group, is warranted to investigate the efficacy of exercise training in this patient subset.

### Other factors

Many other factors may account for the large variability in exercise capacity, such as heterogeneity in native defect leading to Fontan correction, modality of surgical procedure, intracardiac or extracardiac cavopulmonary anastomosis, ability of the surgeons, atrial fenestration, chronic non-cardiac Fontan complications, and genetic factors. Many of these factors, however, cannot be extracted from the papers. Only a multicentre prospective study in a large cohort of patients will allow risk analysis on individual clinical factors.

### Conclusion

Patients with Fontan circulation possess a unique physiological response to exercise. Although there is a wide range in exercise capacity among patients, all patients have reduced tolerance to exercise. Cardiac, pulmonary and muscular factors might play a role in exercise limitation and in the distinct response to exercise.

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