

## **No Synergic Effect of Sildenafil Administration on Exercise Capacity Improvement in a Fontan Patient with Regular Exercise Training**

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### **Authors' contributions**

*This work was carried out in collaboration between all authors. Author AP the training protocol, supervised the training, analyzed the data, and wrote the first draft of the manuscript. Author RS managed the patients training. Author AH designed the study, wrote the study protocol, recruited the patient, and secured the patient's safety. All authors read and approved the final manuscript.*

**Case Study**

**Received 28<sup>th</sup> April 2014**  
**Accepted 16<sup>th</sup> June 2014**  
**Published 27<sup>th</sup> June 2014**

### **ABSTRACT**

In Fontan patients, reduced exercise capacity due to diminished cardiac output is a common finding with important prognostic implications. Beneficial effects have been shown for sildenafil treatment and regular exercise, but data comparing both strategies is scarce. We report on a female patient with Fontan circulation who underwent repeated cardiopulmonary exercise tests with either placebo or a single dose of 50mg sildenafil before and after 6months of supervised aerobic and resistance exercise. At baseline,  $\dot{V}O_2$  peak was 29.1ml/min/kg, and a marked increase to 32.8ml/min/kg was observed after administration of sildenafil. After the training period,  $\dot{V}O_2$  peak was 34.5ml/kg/min in the placebo test, and no further increase by sildenafil was possible (33.7ml/kg/min). Similar results were observed for exercise capacity at the ventilatory anaerobic threshold. In summary, this Fontan patient showed that regular exercise might use up and probably

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exceed the acute sildenafil effects on exercise capacity. Exercise should be considered as a primary treatment strategy within secondary prevention and rehabilitation after the Fontan procedure.

*Keywords: Congenital heart defects; univentricular heart; Fontan circulation; exercise.*

## 1. INTRODUCTION

Sildenafil and exercise training use similar pathways to improve pulmonary vascular function. This case report showed that exercise testing without and with sildenafil might uncover subtle endothelial dysfunction that can be addressed with exercise training.

Most infants born with a single ventricle undergo a kind of Fontan operation that allows long-term survival with an acceptable quality of life. However, the Fontan circulation without subpulmonary ventricle depends on a low pulmonary resistance. A single dose of sildenafil, a phosphodiesterase-5 inhibitor enhancing pulmonary and systemic vasodilating nitric oxide effects, has recently shown to enhance exercise capacity in this patient group [1,2].

As a non-pharmacological approach, regular physical exercise is also well established to improve exercise capacity in several cardiopulmonary disorders, [3] as well as in pulmonary arterial hypertension of congenital heart disease [4]. Similar to sildenafil, exercise activates nitric oxide pathways, thereby improving endothelial function as observed in patients with severe chronic heart failure. Improvements in peak oxygen uptake ( $\dot{V}O_{2peak}$ ) by regular aerobic exercise have also been reported in Fontan patients, but effects of regular exercise were never compared to those from sildenafil. The aim of this case report is to examine whether sildenafil has an additive effect on exercise capacity on top of exercise training.

## 2. METHODS

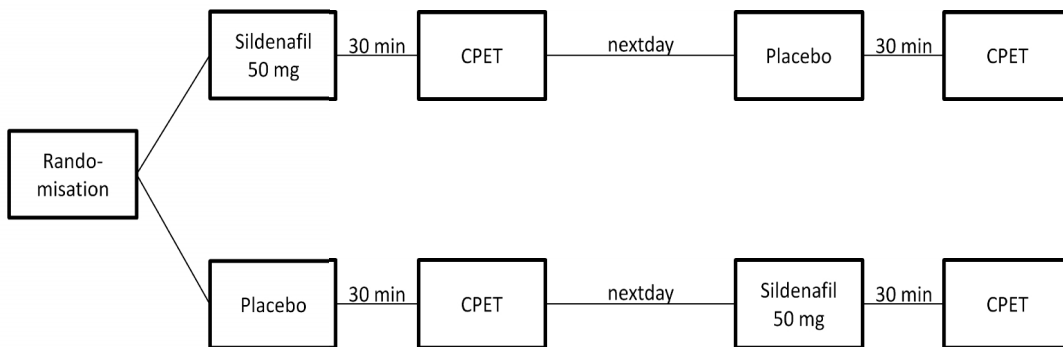
A 20-year old female Fontan patient was referred to the outpatient clinic of sports medicine for 6 months of supervised regular exercise training. She was born with a tricuspid atresia and underwent Fontan-Björk surgery at the age of four years. At her first presentation, the patient was clinically classified as NYHA II; medication consisted of bisoprolol 2.5mg twice daily. Cardiopulmonary exercise testing (CPET) was performed before and six months after the training intervention, as well as after another six months without active intervention (Fig. 1). During each of these three visits the patient underwent two symptom-limited CPET on two consecutive days. Thirty minutes before each test, either 50mg of oral sildenafil or placebo was administered in a randomized and double-blinded fashion. In each of the three study visits the patients was randomized either to a "sildenafil-placebo" or to a "placebo - sildenafil" sequence of the two CPET. CPET were performed on an upright bicycle ergometer using an individualized ramp protocol with an load increase of 15 Watt/min [5]. The first ventilatory threshold (VT) was detected by the V-slope method [6].

The exercise intervention lasted 6months and consisted of supervised aerobic endurance and resistance training twice weekly. After a warm-up of 10minutes, aerobic endurance training was performed on a bicycle over 30minutes starting at an intensity of 60% of maximal heart rate measure in the baseline exercise test. Intensity was slowly increased up to 80% of maximal heart rate depending on the patients comfort. Resistance training was performed on 7 different machines covering all major muscle groups with 3 sets of 10-12

repetitions starting at an intensity of 50% of the particular one repetition maximums and increasing in small steps to 80% of the one repetition maximum. After the resistance training there was a dynamic cool down of 10 minutes with calisthenics.



At each visit



**Fig. 1. Time line**

After the training period of 6 months and reassessment with CPET, the patient was advised to stick to an active life style. No supervised training program was performed anymore.

Prior to study inclusion the patient gave written informed consent. The study was in accordance with the declaration of Helsinki (version 2013) and approved by the local ethical board (project number 2038/08)

### 3. RESULTS

At baseline,  $\dot{V}O_2$  peak and VT from the placebo CPET (29.1ml/kg/min, 19.6ml/kg/min) were enhanced by the single dose of sildenafil (32.8ml/kg/min, 20ml/kg/min).

After 6 months of regular exercise, the initial sildenafil effects were outperformed; the placebo CPET resulted in a higher  $\dot{V}O_2$  peak and VT (34.5ml/kg/min, 24.0ml/kg/min); no further sildenafil-induced increase in exercise capacity could be demonstrated (33.7ml/kg/min; 21.9ml/kg/min).

After another 6 months follow up without active intervention, the exercise effects were almost preserved (33.7ml/kg/min, 21.5ml/kg/min). However, alongside the decrease in regular exercise an additive effect of sildenafil on  $\dot{V}O_2$  peak and VT recurred (35.3ml/kg/min, 22.8ml/kg/min).

More CPET variables and their changes with sildenafil and exercise training are outlined in Table 1.

**Table 1. Cardiopulmonary exercise testing (CPET) without and with sildenafil in a Fontan patient before and after 6 months of exercise training**

CPET placebo/sildenafil	Baseline	After training	After further 6 mo surveillance
<b>Oxygen uptake (<math>\dot{V} O_2</math>)</b>			
@VT [mL/kg/min]	19.6/20.0	24.0/21.9	21.5/22.8
@peak [mL/kg/min]	29.1/32.8	34.5/33.7	33.7/35.3
<b>Heart rate</b>			
@rest [bpm]	62/69	69/56	60 / 54
@VT [bpm]	112/110	103/94	96 / 93
@peak [bpm]	144/149	143/136	134/129
<b>Tidal volume</b>			
@VT [L]	1.03/1.21	1.34/1.40	1.34/1.32
@peak [L]	1.51/1.65	1.64/1.64	1.95/1.93
<b>Resp. Rate</b>			
@VT [/min]	37/33	32/30	30/34
@peak [l/min]	55/50	50/51	45/50
<b>Ventilation (<math>\dot{V}_E</math>)</b>			
@VT [L/min]	38/40	43/42	41/45
@peak [L/min]	66/72	82/84	87/97
$\dot{V}_E/\dot{V} CO_2$ slope	35/35	32/38	30/33
<b>Resting lung function</b>			
FVC [L]	2.79/2.96	2.84/2.95	3.07/3.25
FEV <sub>1</sub> [L]	2.51/2.67	2.50/2.55	2.72/2.87

*VT, ventilatory threshold; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 second*

Clinically, the patient improved to NYHA functional class I, and no exercise-associated adverse events were observed. In all CPET a similar objective exhaustion was indicated by a maximum respiratory exchange ratio of >1.1.

#### 4. DISCUSSION

This case study showed that six months of regular supervised exercise used up and even exceeded the positive sildenafil effects on exercise capacity in a patient with univentricular heart after the Fontan operation.

Exercise uses at least in part similar molecular pathways than sildenafil. Intermittent vascular shear stress induced by exercise activates the endothelial nitric oxide synthase function in the endothelial cell, followed by an increase in nitric oxide. After diffusion into adjacent vascular smooth muscle cells, nitric oxide enhances the production of cyclic guanosine monophosphate (cGMP), resulting in a relaxation and dilation of the vessel and, subsequently, in a decrease of vascular resistance [3]. On the other hand, cGMP is broken down by phosphodiesterase-5. Inhibition of this enzyme by sildenafil similarly results in an enhanced cGMP function in the vascular smooth muscle cells and in an improved vessel relaxation. Thus, both exercise and sildenafil use a common final molecular pathway.

In patients with Fontan circulation cardiac output is limited by a reduced ventricular inflow [7]. This was shown in several echocardiographic [7] and magnetic resonance studies.[8] although hemodynamic evaluations could not measure a significantly elevated pulmonary artery pressure or pulmonary resistance. In an animal model, exercise training could lower

pulmonary vascular resistance in monocrotalin rats with stable pulmonary arterial hypertension [9]. So it could be assumed that exercise training improved the pulmonary NO pathway in our patient leading to an improved ventricular filling. It can even be speculated, that exercise improves endothelial function up to the level of healthy subjects, which lack an improvement in exercise capacity after a single dose of sildenafil at sea level [10].

As the exercise training effects even exceeded the sildenafil effect, it can be speculated that the patient profited additionally from training effects on ventilation or from training effects on the exercising muscle.

## 5. CONCLUSION

In conclusion, in a young female Fontan patient regular supervised aerobic and resistance exercise markedly improved maximal and submaximal exercise capacities, exceeding the effects of a single dose of sildenafil. Thus, there is an urgent need for randomized controlled trials on regular exercise either alone or in addition to sildenafil treatment in Fontan patients.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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