

Wouter Harmsen

# SUBARACHNOID HEMORRHAGE

Physical fitness, physical activity and sedentary behavior  
in the first year post onset





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**Wouter J. Harmsen**

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## **Subarachnoïdale hersenbloeding**

Fysieke fitheid, fysieke activiteit en sedentair gedrag in het  
eerste jaar na een subarachnoïdale hersenbloeding

Proefschrift

ter verkrijging van de graad van doctor aan de  
Erasmus Universiteit Rotterdam  
op gezag van de  
rector magnificus

Prof.dr. H.A.P. Pols

en volgens besluit van het College voor Promoties.  
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Wouter Johannes Harmsen  
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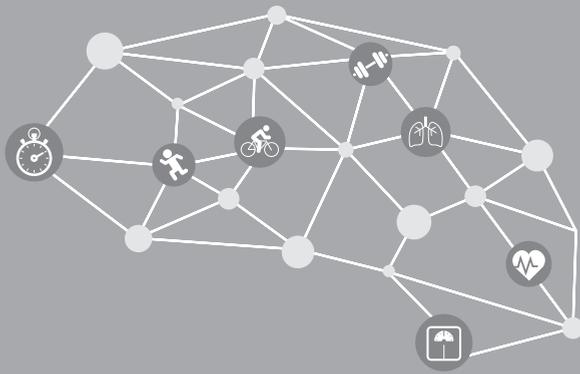
**Promotor:** Prof.dr. G.M. Ribbers

**Overige leden:** Prof.dr. P.J. Koudstaal  
Prof.dr. F. Nollet  
Prof.dr. T.W.J. Janssen

**Copromotoren:** Dr. H.J.G. van den Berg-Emons  
Dr. F. van Kooten

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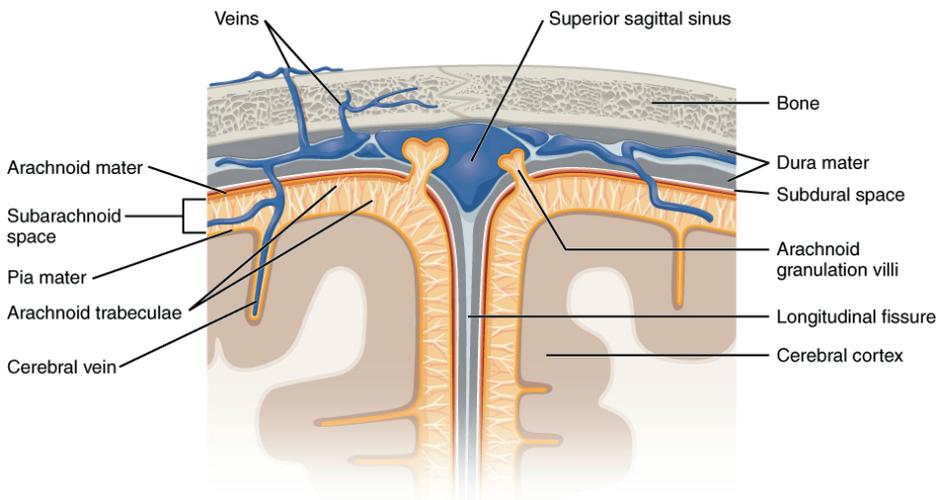
# CHAPTER 1

General Introduction



## SUBARACHNOID HEMORRHAGE

Subarachnoid hemorrhage (SAH) is a subtype of stroke that requires acute medical attention. Hippocrates was probably the first to describe the clinical presentation of SAH (460-370 BC). In his aphorisms on apoplexy he wrote: *'When persons in good health are suddenly seized with pains in the head, and straightway are laid down speechless, and breathe with stertor, they die in seven days, unless fever come on.'*<sup>1</sup> The fact that cerebral aneurysms exist and could rupture was only recognized in the 19<sup>th</sup> century by Dr. Byrom Bramwell.<sup>2</sup> It took until the early 20<sup>th</sup> century until the major symptoms were described, and the term 'spontaneous subarachnoid hemorrhage' was introduced by Sir Charles P. Symonds.<sup>3</sup> Nowadays, a spontaneous SAH refers to the extravasation of blood into the subarachnoid space not resulting from a trauma. The subarachnoid space is the area between the pia mater and arachnoid mater where cerebrospinal fluid circulates (Figure 1). SAH is in approximately 85% caused by a ruptured aneurysm in one of the intracranial arteries, in 10% of the cases it concerns a non-aneurysmal peri-mesencephalic bleeding (centered on the basal cisterns around the midbrain), and in 5% it is caused by a variety of conditions (i.e. cerebral arteriovenous malformations or arterial dissection).<sup>4</sup> This thesis focusses on patients with spontaneous aneurysmal subarachnoid hemorrhage (a-SAH).



**Figure 1.** Representation of a section across the top of the skull, showing the subarachnoid space.

## **EPIDEMIOLOGY**

The incidence of a-SAH has remained stable over the last few decades and is approximately 9 per 100,000 persons per year, and accounts for 5% of all stroke cases.<sup>4</sup> Because it strikes at a fairly young age (on average 55 years), the total loss of productive life years is almost similar to that for cerebral ischemia or intracerebral haemorrhage.<sup>5</sup> Advances in diagnostics and neurosurgical treatment have increased the chance of surviving an a-SAH and today's survival rate reaches 65%.<sup>6</sup> Since more patients survive the acute phase, it has become increasingly important to understand the long-term consequences of a-SAH.

## **CLINICAL MANIFESTATION, DIAGNOSIS AND TREATMENT**

The classical feature of a-SAH is a severe headache with an acute onset (i.e. thunderclap headache). Additional symptoms are vomiting, nausea, loss of consciousness, stiff neck, and sometimes seizures.<sup>7</sup> The diagnosis is confirmed by computerized tomography (CT) of the brain and in cases with negative CT by lumbar puncture. Once the diagnosis has been confirmed, immediate intervention is required aiming at cardiovascular stabilization and securing the ruptured aneurysm. The traditional method of treatment is neurosurgical clipping, which was first performed by neurosurgeon W.E. Dandy in 1937.<sup>8</sup> It is an invasive procedure involving craniotomy followed by the placement of a clip around the neck of the aneurysm. Advances in neurosurgical techniques have led to the introduction of endovascular coiling by neurosurgeon G. Guglielmi in 1991.<sup>9</sup> In endovascular coiling, a catheter is led via the femoral artery to the parent artery where the aneurysm is located. When the platinum coils react with the blood, thrombosis occurs which will stop the circulation in the aneurysm. Endovascular coiling has evolved to be the preferential treatment and gives better clinical outcome than neurosurgical clipping in most patients with a-SAH.<sup>10</sup>

## **OUTCOME OF SUBARACHNOID HEMORRHAGE**

Of all patients who survive the initial weeks, 85% will regain independence in basic activities of daily living.<sup>11, 12</sup> However, the incidence of clinical deficits may be higher than previously thought.<sup>13</sup> Fatigue is the most frequently reported complaint (reported in 30-91%), and may be present up to seven years post onset.<sup>14</sup> Half of the patients have symptoms of anxiety and depression in the second year and disturbances in executive functioning and mood have been reported at four years post a-SAH.<sup>12, 14, 15</sup> These long term sequelae can have a detrimental impact on daily living, with approximately half of

the patients not being able to resume previous activities, and only one-third being able to fully return their previous occupation.<sup>16,17</sup> Especially, because patients with a-SAH are relatively young, these restrictions can have a long-lasting impact on daily life.

Since fatigue plays an overwhelming role in daily life of most survivors,<sup>14</sup> patients may be at risk of low fitness with physical inactive and sedentary lifestyles. Durstine et al. hypothesized that fatigue, fitness and physical activity interact with each other, and that fatigue can easily lead to a vicious circle of deconditioning.<sup>18</sup> Low fitness and physical inactivity have been frequently reported in chronic conditions, and seem to play an important role in the long-term outcomes.<sup>18</sup> Studies on physical fitness, physical activity or sedentary behavior are lacking in a-SAH. This may be since it is assumed that most a-SAH patients have a favorable outcome, and therefore they have frequently been excluded from stroke rehabilitation research. Insights in the levels of physical fitness, physical activity and sedentary behavior may contribute in understanding the consequences of a-SAH and in improving rehabilitation programs.

In this thesis, we focus on physical fitness, physical activity and sedentary behavior in the first year after a-SAH. Being physically fit is defined as ‘having the ability to carry out daily activities with vigor and alertness, without undue fatigue and with ample energy to enjoy leisure time activities, and to meet unforeseen emergencies’.<sup>19</sup> Physical fitness is a major contributor to a healthy lifestyle particularly because of its ‘inverse relationship to all-cause mortality.’<sup>20</sup> Physical fitness is believed to be a prerequisite for optimizing and maintaining physical activities in daily life,<sup>19</sup> and the prevention of secondary health complications.<sup>18, 21</sup> Physical activity and sedentary behavior are two distinct constructs of physical behavior.<sup>22</sup> Physical activity refers to ‘any bodily movement produced by skeletal muscles that requires energy expenditure’ and contributes to the primary and secondary prevention of chronic diseases, including cardiovascular disease, cancer, diabetes mellitus, hypertension and obesity.<sup>19, 23</sup> Sedentary behavior refers to activities that require low levels of energy expenditure and involve sitting and lying activities during waking hours.<sup>28</sup> Sedentary behavior negatively impacts metabolism and cardiovascular health, independent of the volume of physical activity.<sup>24, 25</sup> Consequently, sufficient physical activity with little sedentary behavior is recommended for optimal health.<sup>23, 26</sup>

A better understanding of physical fitness, physical activity and sedentary behavior may hold important implications for rehabilitation in a-SAH. Rehabilitation has the potential to minimize the consequences of a disease with the ultimate goal of restoring participation. Physical fitness, physical activity, and sedentary behavior are known targets to improve health in the general population and in different patient populations, including patient with hemorrhagic or ischemic stroke.<sup>18, 23, 26, 27</sup> Furthermore, higher levels of

physical fitness may provide a physical reserve to fatigue, and a margin of safety during physical demanding activities.<sup>18,23</sup> However, studies on physical fitness, physical activity and sedentary behavior are lacking in a-SAH.

## AIM OF THIS THESIS

The goal of this thesis was to gain insights in the level of physical fitness, physical activity and sedentary behavior in the first year after a-SAH. Objective measures of fitness, activity and sedentary behavior were collected at six and twelve months post a-SAH and compared to that of sex and age-matched controls. Follow-up was applied to study changes in fitness, activity and sedentary behavior over time. Furthermore, we explored whether physical deconditioning (i.e. low fitness and inactive and sedentary lifestyles) plays a role in fatigue, and whether we could identify subgroups at risk of poor outcomes.

## OUTLINE THESIS

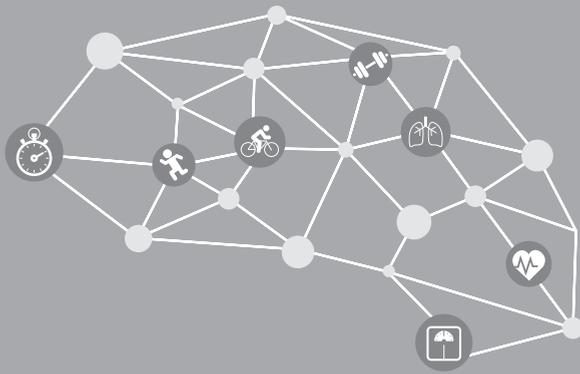
This thesis describes the results of a one-year follow-up study on physical fitness, physical activity and sedentary behavior in patients with a-SAH. **Chapter 2** evaluates physical activity and sedentary behavior of patients at six months post a-SAH. Different types of physical activity and sedentary behavior were distinguished, the total volume of physical activity and sedentary behavior determined, and distribution metrics analyzed. Outcome measures were compared to that of a sex- and age-matched comparison group. **Chapter 3** describes results regarding the isokinetic knee muscle strength at six months post a-SAH. Patients were individually matched to a healthy control based on sex and age. Since fatigue is one of the most distressing complaints in a-SAH, maximal isokinetic knee muscle strength has been explored in fatigued and non-fatigued patients. **Chapter 4** provides insights into the cardiorespiratory fitness of patients at six months post onset. Progressive cardiopulmonary exercise testing (CPET) was performed from which the peak oxygen uptake ( $\dot{V}O_{2\text{peak}}$ ) was determined. The cardiorespiratory fitness of patients was compared to that of sex- and age-matched controls. **Chapter 5** describes whether the six-minute walk test (6MWT) is a valid alternative to progressive CPET, in order to predict  $\dot{V}O_{2\text{peak}}$  in a-SAH. **Chapter 6** evaluates follow-up measures of physical fitness, and explores relationships between fitness and physical activity, sedentary behavior and functional outcome. Further, it aims to identify patients at risk of low fitness by evaluating disease-related characteristics. **Chapter 7** describes the prevalence of fatigue over the first year, and explores whether physical deconditioning, as reflected by low fitness and inactive and sedentary lifestyles, plays a role in fatigue.

Secondary, it explores whether the severity of fatigue could be predicted by disease-related characteristics which may help to target future interventions. **Chapter 8** is the general discussion of this thesis and presents the main findings, discusses unanswered questions and proposes future research directions and clinical implications.

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# CHAPTER 2

## Inactive lifestyles and sedentary behavior in persons with aneurysmal subarachnoid hemorrhage: evidence from accelerometer-based activity monitoring

Wouter J. Harmsen, Gerard M. Ribbers, Majanka H. Heijenbrok-Kal, Johannes B.J. Bussmann, Emiel S. Sneekes, Ladbou Khajeh, Fop van Kooten, Sebastian J. Neggers, Rita J.G. van den Berg-Emons

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## ABSTRACT

**Background:** Aneurysmal subarachnoid hemorrhage (a-SAH) is a potential life-threatening stroke. Because survivors may be at risk of inactive and sedentary lifestyles, this study evaluates physical activity (PA) and sedentary behavior (SB) in the chronic phase after a-SAH.

**Methods:** PA and SB were objectively measured at six months post a-SAH with an accelerometer-based activity monitor, with the aim to cover three consecutive weekdays. Total time spent in PA (comprising walking, cycling, running and non-cyclic movement) and SB (comprising sitting and lying) was determined. Also, in-depth analyses were performed to determine the accumulation and distribution of PA and SB throughout the day. Binary time series were created to determine the mean bout length and the fragmentation index. Measures of PA and SB in persons with a-SAH were compared to that of sex- and age-matched healthy controls.

**Results:** The 51 participants comprised 33 persons with a-SAH and 18 controls. None of the participants had signs of paresis or spasticity. Persons with a-SAH spent 105 min/24 h being physically active, which was 35 min/24 h less than healthy controls ( $p=0.005$ ). For PA, compared with healthy controls, the mean bout length was shorter in those with a-SAH (12.0 vs. 13.5 sec,  $p=0.006$ ) and the fragmentation index was higher (0.053 vs. 0.041,  $p<0.001$ ). There were no significant difference between groups for total SB during waking hours (514 min vs. 474 min,  $p=0.291$ ). For SB, the mean bout length was longer in persons with a-SAH (122.3 vs. 80.5 sec,  $p=0.024$ ), whereas there was no difference between groups for the fragmentation index (0.0032 vs. 0.0036,  $p=0.396$ ).

**Conclusions:** Persons with a-SAH are less physically active, they break PA time into shorter periods, and SB periods last longer compared to healthy controls. Since inactive lifestyles and prolonged uninterrupted periods of SB are independent risk factors for poor cardiovascular health, interventions seem necessary and should address both PA and SB.

## INTRODUCTION

Aneurysmal subarachnoid hemorrhage (a-SAH) is caused by a bleeding of a ruptured aneurysm which leads to the extravasation of blood into the subarachnoid space.<sup>1</sup> It accounts for 5% of all stroke cases and has an incidence rate of 9 per 100,000 persons per year and a mortality rate of 50%.<sup>1,2</sup> Persons with a-SAH are relatively young compared with patients with ischemic or hemorrhagic stroke (55 years vs. 70 years).<sup>1,3</sup> Further, whereas ischemic or hemorrhagic stroke may lead to focal brain damage with specific stroke-related symptoms, brain damage in a-SAH has a more diffuse character without typical stroke symptoms.<sup>1</sup> Those who survive an a-SAH are likely to experience long-term symptoms, such as cognitive problems (40%), emotional complaints (50%), depressive symptoms (40%), and fatigue (up to 91%).<sup>4-7</sup> Even among those who are classified as having a 'favorable outcome', the incidence of clinical deficits is high.<sup>8</sup>

Persons with a-SAH seem to have difficulty with resuming their premorbid daily activities, and only one-third is able to fully resume their previous occupation.<sup>4,9</sup> The inability to perform daily activities may be a consequence of passive coping styles, depressive symptoms and fatigue.<sup>6,8-10</sup> Reduced physical fitness after a-SAH has been reported,<sup>11</sup> which may also hinder the performance of daily physical activities. Therefore, individuals with a-SAH may be at risk of inactive and sedentary lifestyles, placing them at risk of poor health outcomes.<sup>12-14</sup> However, measures of daily PA and SB have not yet been studied in patients with a-SAH.

PA refers to '*any bodily movement produced by skeletal muscles that requires energy expenditure*' and contributes to the primary and secondary prevention of chronic diseases, including cardiovascular disease, cancer, diabetes mellitus, hypertension and obesity.<sup>15,16</sup> SB, defined as a distinct class of activities that requires low levels of energy expenditure and involves sitting and lying activities during waking hours, negatively impacts metabolism and cardiovascular health.<sup>17,18</sup> Recent studies show that SB impacts cardiovascular health, independent of the volume of PA.<sup>18</sup> Further, not only the total volume of PA or SB, but also the way PA and SB are accumulated seems to be important, i.e. prolonged bouts of PA are beneficial, whereas prolonged bouts of SB are found to be detrimental to cardiovascular health.<sup>18-21</sup>

Persons with stroke not caused by a-SAH are highly sedentary, with PA levels almost half that of healthy control subjects.<sup>22-24</sup> In stroke rehabilitation, improving PA and SB is strongly recommended, as it provides protective benefits in the primary and secondary prevention of chronic diseases.<sup>16,25</sup> Inactive and sedentary lifestyles in ischemic or hemorrhagic stroke have been frequently explained in terms of motor impairment following

neuro-motor lesions. Since brain damage in a-SAH is more diffuse without typical stroke symptoms (such as paresis), it would be of interest to gain insight in the level of PA and SB in this patient group.

Despite its importance, PA and SB have not yet been studied in persons with a-SAH. Therefore, this study evaluates PA and SB in a-SAH. Objectively obtained measures of PA and SB were compared to those in sex- and age-matched healthy controls. This study can help to optimize recommendations to prevent chronic diseases and debilitating conditions after a-SAH, but can also be used to better understand the effects of different types of stroke on daily PA and SB. Since individuals with a-SAH have difficulty in resuming their daily activities and have reduced physical fitness, we hypothesized that they would be less physically active and more sedentary compared to healthy controls.

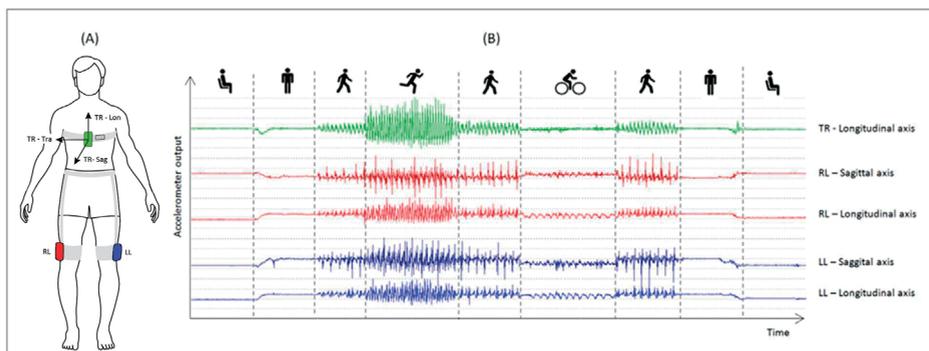
## **METHODS**

### **Participants and study design**

The present study (entitled HIPS-Rehab) was part of the 'Hypopituitarism In Patients after Subarachnoid hemorrhage (HIPS) study'.<sup>26</sup> In this study we investigate PA and SB in persons who were six months post a-SAH. Participants with a-SAH admitted to the department of Neurology of Erasmus University MC were eligible for inclusion if they were aged  $\geq 18$  years. Diagnosis of a-SAH was confirmed by computerized tomography (CT) of the brain and, in cases with negative CT, by lumbar puncture. Exclusion criteria were: hypothalamic or pituitary disease diagnosed prior to a-SAH, history of cranial irradiation, trauma capitis prior to a-SAH, other intracranial lesion apart from a-SAH, and other medical or psychiatric condition or laboratory abnormality that may interfere with the outcome of the study. Participants were also excluded if they were aged  $\geq 70$  years. For comparison, we included healthy controls of similar sex (females; 64% vs. 72%,  $p=0.382$ ) and age (52.6 vs. 51.0 years,  $p=0.548$ ). Healthy controls were recruited by advertisement; controls wore identical activity monitors and similar measurement procedures were applied. The study was approved by the Medical Ethics Committee of Erasmus University Medical Centre, and all participants provided written informed consent.

### **Physical activity and sedentary behavior**

Physical activity (PA) and sedentary behavior (SB) were objectively measured with an accelerometer-based activity monitor (VitaMove, 2M Engineering, Veldhoven, the Netherlands) (Figure 1). This monitor has demonstrated validity for quantifying body postures and movements in healthy subjects and in different patient groups.<sup>27-29</sup>



**Figure 1.** Placement of the VitaMove activity monitor is shown in (A), and a typical output derived from the raw accelerometer signals is presented in (B). The pattern of these signals determines corresponding activities. A sequence of activities is presented: sitting, standing, walking, running, walking, cycling, walking, standing and sitting.

Abbreviations: TR=Trunk sensor; RL=Right leg sensor; LL=Left leg sensor; Lon=longitudinal axis; Sag=sagittal axis; Tra=transversal axis.

The VitaMove activity monitor consists of three individual body-fixed recorder units, which are wirelessly connected and synchronized every 10 seconds. One recorder unit was attached to the trunk (sternum position) and one to each thigh, using specially developed elastic belts. Each unit has its own tri-axial accelerometer (Freescale MMA7260Q, Denver, USA), power supply and storage capacity. Participants wore the VitaMove on consecutive weekdays, except during swimming, bathing and sleeping. In line with previous research, the intended duration of measurement was three consecutive days, with a minimum of one day.<sup>30,31</sup> Further, the signal processing parameters were identical to the parameter settings of the validity studies.<sup>27-29</sup> Mean values were calculated for multiple days of activity monitoring. Participants were instructed to continue their ordinary daily activities. The principles of the measurements were explained after all measurements were completed to avoid measurement bias. In addition, participants kept activity diaries to report reasons of non-wear periods of the activity monitor.

### Data processing

Accelerometer signals of each recorder unit were continuously measured and stored (128 Hz) on a micro Secure Digital memory card. Accelerometer signals were downloaded on a computer for kinematic analyses using specially developed VitaScore software (VitaScore BV, Gemert, the Netherlands). Waking hours were determined by the researcher (WH) using the diaries filled out by the participants and by inspection of the raw data signals; specifically, ongoing flatlines indicate that the recorder units were taken off. Body postures and movements (e.g. lying, sitting, standing, walking, cycling, running and non-cyclic movements) were automatically detected with a 1-second time resolution from the feature time series (i.e. angle, frequency and motility) derived from

the measured accelerometer signals. The motility feature expresses the intensity of the movement of the body segment to which the unit is attached, and depends on the variability of the acceleration signal; motility can be compared to counts that are calculated in regular activity monitors (calculated in gravitational force (g), 1 g=9.81 m/s<sup>2</sup>). During walking, the body motility signal (i.e. the mean of the leg and trunk motility signals) corresponds to walking speed.<sup>32</sup> The minimum duration threshold for each activity was 5 seconds. A detailed description of the algorithms and analysis is published elsewhere.<sup>28,30</sup>

In-depth analyses were performed to quantify the accumulation and distribution metrics of PA and SB. For PA, the four detected body movements (walking, cycling, running, and non-cyclic movements) were categorized into one PA category; a similar procedure was followed for SB (covering lying and sitting activities). Binary time series of either PA (yes=1, no=0) and SB (yes=1, no=0) were created using custom-made MATLAB algorithms. A period of uninterrupted samples of PA (or SB) was classified as a bout. Due to the minimum duration threshold of 5 seconds, bouts and periods between bouts lasted at least 5 seconds.

## **Outcome measures**

### *Volume, intensity and distribution of PA and SB*

To determine the volume of PA, we calculated the total time spent in the four detected body movements during waking hours. The volume of total SB was determined by evaluating the total time of sitting and lying activities during the waking hours. Volume measures were then expressed as a percentage of a 24h period, and as a percentage of waking hours. The mean motility of PA and the mean motility of walking were also determined and expressed in g (1 g=9.81 m/s<sup>2</sup>).

Binary time series were used to determine the accumulation and distribution of either PA and SB. The total number of bouts and mean bout length (in seconds) were calculated. Since the mean bout length was not normally distributed, the natural logarithm was taken. The mean log length was back transformed to the original scale. The fragmentation index was calculated and reflects the ratio between the number of PA (or SB) bouts divided by the total PA (or SB) time.<sup>33</sup> A higher fragmentation index indicates that total PA (or SB) time is more fragmented, which means that there are less prolonged periods of PA (or SB).<sup>34</sup>

### *Participants' characteristics*

At hospital intake, the following clinical characteristics were obtained including: 1) the severity of a-SAH according to the grading of the World Federation of Neurologic Surgeons (low-grade: I-III or high-grade: IV-V)<sup>35, 36</sup> and the Glasgow Coma Scale (GCS) score,<sup>37</sup> 2) location of the aneurysm (anterior or posterior circulation), 3) treatment pro-

cedure (surgical clipping or endovascular treatment), 4) presence of secondary health complications (re-bleed, delayed cerebral ischemia, hyponatremia, hydrocephalus and growth hormone deficiency; defined as an insufficient growth hormone (GH) response to a GH-releasing hormone -arginine test),<sup>38</sup> and 5) neurologic comorbidity (paresis or spasticity). Neurologic morbidity (such as paresis or spasticity) was evaluated by treating neurologist. Information on the following characteristics and body anthropometrics were collected from both groups: sex, age, weight, height and Body Mass Index (BMI).

### Statistical analyses

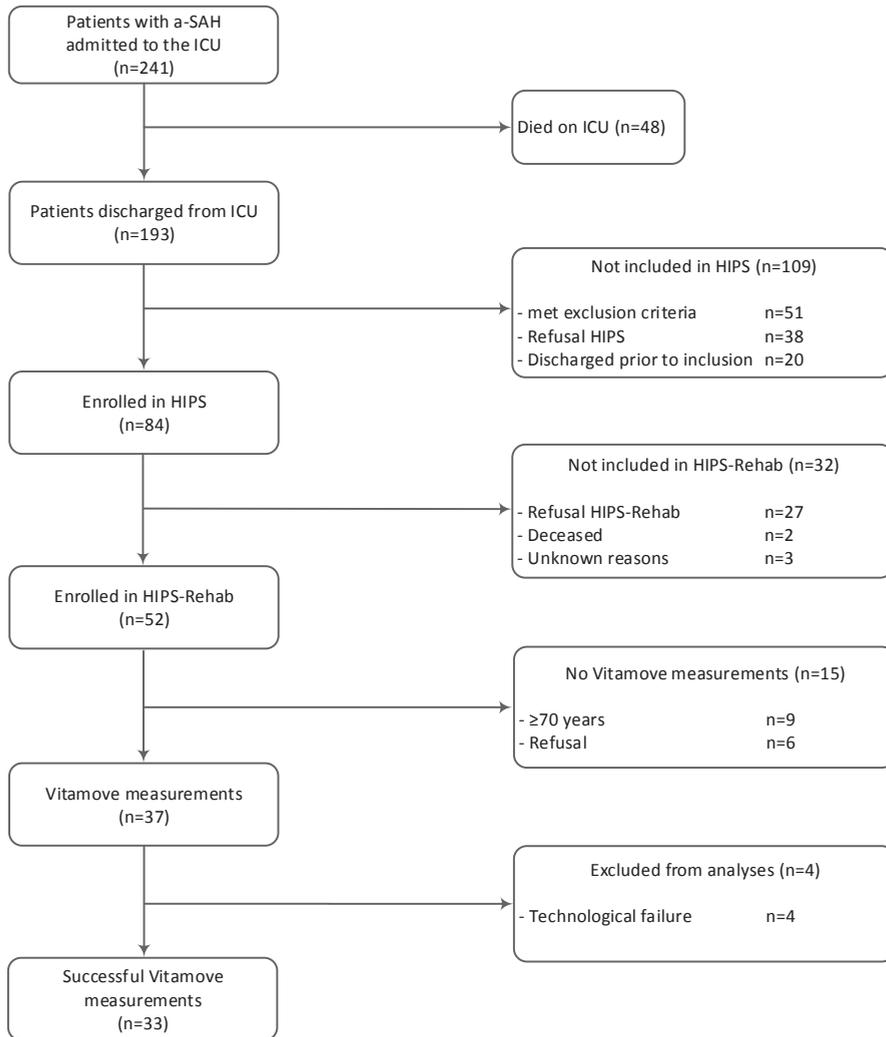
All data are expressed as mean (SD) unless otherwise indicated. To compare the clinical characteristics between participants of HIPS-Rehab and those who did not participate (but included in HIPS), we used independent t-tests for continuous data and chi-square-tests for categorical data. To compare the characteristics and measures of physical behavior between individuals with a-SAH and controls, independent t-tests were applied for continuous data and chi-square tests for categorical data. All analyses were performed using IBM SPSS Statistics, version 20. A probability value of  $p < 0.05$  was considered statistically significant.

## RESULTS

Of the 241 patients admitted to the ICU with a diagnosis of a-SAH, 84 were included in HIPS of which 52 volunteered to participate in HIPS-Rehab. Participants in HIPS-Rehab ( $n=52$ ) did not differ from those who did not participate (but included in HIPS;  $n=32$ ) regarding the severity of a-SAH, location of the aneurysm, treatment procedure, and the presence of secondary health complications (data not presented). Of the 52 participants, successful activity monitoring measurements were obtained from 33: of the 19 unsuccessful attempts, six refused to wear the activity monitor, in four persons data processing was unsuccessful due to technological failure, and 9 were aged  $\geq 70$  years (Figure 2).

Table 1 presents the clinical characteristics. Most persons with a-SAH underwent endovascular coiling (82%) and most had a lesion in the anterior circulation (61%). The neurological scores showed that 29 participants had a low-grade a-SAH (88%) and a mean GCS-score of 14.0 (SD 2.0). None of the participants had a paresis or showed signs of spasticity.

Due to challenges with activity monitoring, data were not available for all participants for the intended three days of measurement. The duration of measurement was 3 days



**Figure 2.** Consort flow diagram

in 42% of the patients and in 83% of the controls; 2 days in 48% of the patients and in 6% of the controls; and 1 day in 9% of the patients and in 11% of the controls. Mean daily wear time did not differ between groups, 13.7 h (SD 1.8) vs. 14.1 h (SD 1.3), respectively, (95% CI of the difference: -1.4 h to 0.5 h;  $p=0.372$ ).

Table 2 presents the characteristics of the two groups: persons with a-SAH did not differ from healthy controls regarding sex ( $p=0.382$ ), age ( $p=0.548$ ), weight ( $p=0.231$ ) and height ( $p=0.062$ ), but had a higher BMI ( $p=0.002$ ). Table 2 also presents the volume measures of PA and SB in the two groups. Persons with a-SAH spent 105 min/24 h (7.3%)

**Table 1.** Descriptive characteristics.

Characteristics	Participants with a-SA-H (n=33)
Sex, female, n (%)	21 (64)
Age (years), mean (SD)	52.6 (9.0)
WFNS grade, n (%)	
I	16 (48)
II	13 (39)
III	1 (3)
IV	3 (9)
V	0 (-)
Glasgow Coma Scale score, mean (SD)	14.0 (2.0)
Location aneurysm, n (%)	
- Anterior circulation	20 (61)
- Posterior circulation	13 (39)
Aneurysm treatment, n (%)	
- Endovascular coiling	27 (82)
- Surgical clipping	6 (18)
Complications, n (%)	
- Re-bleed	0 (-)
- Delayed cerebral ischemia	7 (21)
- Hyponatremia	4 (12)
- Hydrocephalus	9 (27)
- Growth Hormone Deficiency	2 (6)

Abbreviations: WFNS grade, World Federation of Neurologic Surgeons grading system for subarachnoid hemorrhage.

being physically active, which is 35 min/24 h (2.4%) less compared with that of healthy controls (140 min/24 h (9.7%);  $p=0.005$ ); in particular, patients participated less in cycling activities (3 min/24 h (0.2%) vs. 27 min/24 h (1.9%);  $p<0.001$ ).

Total sedentary time did not differ between those with a-SA-H and healthy controls; 514 min/24 h (35.7%) vs. 473 min/24 h (32.9%);  $p=0.291$ ), respectively. Also, there was no difference between groups for total standing time, i.e. 200 min/24 h (13.9%) vs. 233 min/24 h (16.2%);  $p=0.164$ ), mean PA motility and mean walking motility ( $p=0.442$  and  $p=0.503$ , respectively).

Mean bout length of PA in persons with a-SA-H was shorter than in controls (12.0 sec vs. 13.5 sec;  $p=0.006$ ), and the PA fragmentation index was higher (0.053 vs. 0.041;  $p<0.001$ ), indicating that PA periods were shorter, and that total time spent in PA was

**Table 2.** Characteristics and results of activity monitoring measurement.

Characteristics	Participants with a-SAH (n=33)	Healthy controls (n=18)	95% CI of the difference	p-value
Sex, females, n (%)	21 (64)	13 (72)	-	0.382
Age (years), mean (SD)	52.6 (9.0)	51.0 (8.6)	-3.7 to 6.8	0.548
Weight (kg), mean (SD)	75.6 (13.0)	71.4 (9.1)	-2.7 to 11.1	0.231
Height (m), mean (SD)	1.67 (0.1)	1.72 (0.1)	-11.7 to 0.3	0.062
BMI (kg/m <sup>2</sup> ), mean (SD)	27.1 (3.8)	23.9 (2.0)	1.2 to 4.7	0.002
<b>Activity profiles<sup>a</sup>, mean (SD)</b>				
% Physical activity	7.3 (3.0)	9.7 (2.1)	-3.9 to -0.8	0.005
- % Walking	4.7 (2.4)	4.7 (1.3)	-1.2 to 1.3	0.964
- % Cycling	0.2 (0.4)	1.9 (1.7)	-2.3 to -1.1	<0.001
- % Running	0.0 (0.0)	0.1 (0.3)	-0.2 to -0.02	0.018
- % Non-cyclic movement	2.4 (1.7)	3.0 (1.1)	-1.5 to 0.3	0.200
% Standing	13.9 (5.4)	16.2 (5.7)	-5.6 to 1.0	0.164
% Sedentary behavior	35.7 (9.9)	32.9 (7.6)	-2.5 to 8.3	0.291
- % Sitting	32.5 (10.1)	30.7 (7.7)	-3.6 to 7.3	0.502
- % Lying	3.2 (3.5)	2.2 (1.8)	-0.8 to 2.8	0.253
% Non-wear <sup>b</sup>	43.0 (7.3)	41.2 (5.6)	-2.2 to 5.8	0.372
<b>Intensity, mean (SD)</b>				
Motility physical activity (g) <sup>c</sup>	45.6 (11.9)	47.8 (8.6)	-7.5 to 3.3	0.442
Motility walking (g) <sup>c</sup>	37.6 (9.9)	39.7 (7.7)	-8.6 to 4.3	0.503

Note: Duration of activities as a percentage of 24 hours.

<sup>a</sup> Physical behavior was monitored on consecutive weekdays in the free-living situation;

<sup>b</sup> Non-wear is the time that participants did not wear the activity monitor (also reflects nighttime);

<sup>c</sup> g=gravitational forces \*100.

**Table 3.** Distribution of physical activity and sedentary behavior.

Distribution metrics mean (SD)	Participants with a-SAH (n=33)	Healthy controls (n=18)	95% CI of the difference	p-value
<b>Physical activity</b>				
Mean bout length (s) <sup>a</sup>	12.0 (1.9)	13.5 (1.2)	-2.4 to -0.4	0.006
Fragmentation index <sup>b</sup>	0.053 (0.01)	0.041 (0.01)	0.006 to 0.019	<0.001
<b>Sedentary Behavior</b>				
Mean bout length (s) <sup>a</sup>	122.3 (71.5)	80.5 (35.6)	5.6 to 78.0	0.024
Fragmentation index <sup>b</sup>	0.0032 (0.002)	0.0036 (0.002)	-0.001 to 0.001	0.396

Note: The minimum bout length lasted at least 5 seconds. <sup>a</sup> Uninterrupted bouts with a minimum length of 5 seconds. <sup>b</sup> Fragmentation index represents the ratio between the number of sedentary bouts divided by the total time being sedentary.

more fragmented in persons with a-SAH. Mean bout length of SB was longer in persons with a-SAH (122.3 sec vs. 80.5 sec; p=0.024), whereas the SB fragmentation index did not

differ between groups ( $p=0.396$ ). This indicates that SB periods lasted longer in persons with a-SAH, but the way in which total SB was distributed did not differ between groups (Table 3).

## DISCUSSION

The present study shows that persons with a-SAH have physically inactive and sedentary lifestyles, placing them at increased risk for poor health outcomes.<sup>12-14</sup> Persons with a-SAH are less physically active, they break PA time into shorter periods, and SB periods last longer compared to healthy controls. This is the first study on PA and SB in persons with a-SAH. The objectively obtained measures of PA and SB have meaningful implications in stroke rehabilitation because our findings reveal that inactive and sedentary lifestyles are present in absence of motor impairments. Given the importance of optimal PA and SB,<sup>21, 22</sup> therapeutic interventions are warranted. The present findings may help to improve interventions (targeting both PA and SB) in order to prevent debilitating conditions in a-SAH.

In-depth analysis of PA revealed that persons with a-SAH break their PA time into shorter periods, which is not beneficial from a health perspective.<sup>21</sup> These interruptions may be explained by an increased number of moments of rest, possibly related to higher fatigability, cognitive dysfunction, and/or lower cardiorespiratory fitness.<sup>5, 7</sup> The most recent guidelines of the WHO recommend an accumulation of PA time, i.e. uninterrupted PA of at least 10 minutes, as this is an important aspect of healthy PA.<sup>39</sup> Therefore, therapeutic interventions should not only target the total volume of PA, but should also improve the accumulation of PA time in persons with a-SAH.

Sedentary time, particularly accumulated in long uninterrupted periods, negatively impact cardiovascular health, independent of the volume of PA.<sup>18</sup> In-depth analysis of SB revealed that SB periods lasted longer in persons with a-SAH. However, the SB fragmentation index did not differ, indicating that the way total SB is distributed in a-SAH is similar to that in healthy controls. This could be explained by the fact that the total sedentary time was somewhat higher (albeit not significant) in a-SAH than in healthy controls. Since SB periods lasted longer in those with a-SAH than in controls, breaking prolonged uninterrupted SB periods may represent another therapeutic target to provide additional health benefits in persons with a-SAH.

In patients with stroke not caused by a-SAH, the most commonly used objective measures of PA are step or activity counts per day; these counts are reported to be almost half

those of healthy controls.<sup>22-24</sup> The present study explored activity profiles beyond simple step or activity counts and distinguished different types of PA. Overall, persons with a-SAH spent 25% less time in PA than healthy controls (105 vs. 140 min/24 h, respectively). However, the total volume of walking activities did not differ between groups; this is in line with an accelerometer-based study on walking activities in patients with stroke.<sup>40</sup> Furthermore, compared with controls, persons with a-SAH participated particularly less in cycling activities and, to a lesser extent, in running activities.

Interestingly, physically inactive and sedentary lifestyles after a-SAH seem not be related to motor impairments like in patients with ischemic or hemorrhagic stroke, and therefore other mechanisms should underlie our findings. For example, PA may be limited by impaired cardiorespiratory fitness, cognitive dysfunction, anxiety or fatigue. Feelings of anxiety after a-SAH can highly restrict participation in daily activities.<sup>41, 42</sup> Furthermore, PA can also be limited by concentration problems,<sup>5, 43, 44</sup> e.g. cycling activities are more demanding due to participation in traffic and multitasking. However, future studies are warranted to investigate the barriers and facilitators of PA after a-SAH, and should take into account mechanisms of physical deconditioning, cognitive dysfunction, anxiety and fatigue.

In persons with a-SAH, total sedentary time during waking hours was 514 minutes. This is similar to findings in persons with stroke, not caused by a-SAH (i.e. sedentary times ranging from 464-654 minutes).<sup>23, 24</sup> This is remarkable because patients with a non a-SAH stroke are often older and more restricted in the performance of daily activities (often because of neuro-motor deficits) than patients with a-SAH.<sup>1, 6</sup> With regard to SB, there are no guidelines for the general population. A meta-analysis showed that above 7.0 h, every additional hour increase in SB time is associated with a 5% increase in all-cause mortality.<sup>45</sup> In the present study, individuals with a-SAH spent about 8.5 h being sedentary, implying a 7.5% increase in all-cause mortality. In order to set therapeutic targets, additional studies are needed to establish guidelines for SB.

The major strength of the present study is the objective measurement of PA and SB, without possible bias from the subjective character of questionnaires. Also, the inclusion of healthy controls allowed us to better interpret the data. Another strength is that we used innovative in-depth analyses of PA and SB which provides new insights to support future therapeutic interventions.

### **Study limitations**

Some limitations of the present study should be discussed. First, we used an advanced activity monitor that allowed to obtain continuous data on various types of PA and SB.

However, this makes it difficult to compare our data with general guidelines for healthy PA or SB, because these guidelines are mostly based on self-report questionnaires.<sup>29</sup> Future studies need to define guidelines for healthy PA and SB, based on objectively obtained measures. Second, for logistic reasons, the sample size of healthy controls was smaller compared to that in persons with a-SAH. Smaller number of controls have been frequently reported in activity monitoring research across different patient groups, including stroke.<sup>46, 47</sup> Overall, results on the main outcome (volume metrics) in the controls are comparable with, and for PA even somewhat lower (9.7% vs. 10-12% per 24h, respectively) than results, as measured with the VitaMove, in other healthy comparison groups.<sup>48-50</sup> This difference may even indicate that we have underestimated the lack of PA in persons with a-SAH. BMI was somewhat higher in persons with a-SAH than in controls. However, it was not feasible to account for BMI, as a higher BMI may already be indicative of physically inactive and sedentary lifestyles. Another limitation is that, in both groups, actually 'wearing' the activity monitor may have influenced PA in daily life; nevertheless, all participants reported that they performed their regular PA. Another limitation is that we did not include any physiological parameters (e.g. heart rate) that might have provided more details on physical strain of PA in daily life.

## CONCLUSIONS

Objectively obtained measures of PA and SB show that persons with a-SAH are less physically active, they break PA time into shorter periods, and SB periods last longer compared to healthy controls. These results suggest that persons with a-SAH have increased health risks related to inactive and sedentary lifestyles. Given the importance of optimal PA and SB, future studies need to identify barriers and facilitators of PA and SB to optimize therapeutic interventions with the goal to improve PA and SB after a-SAH.

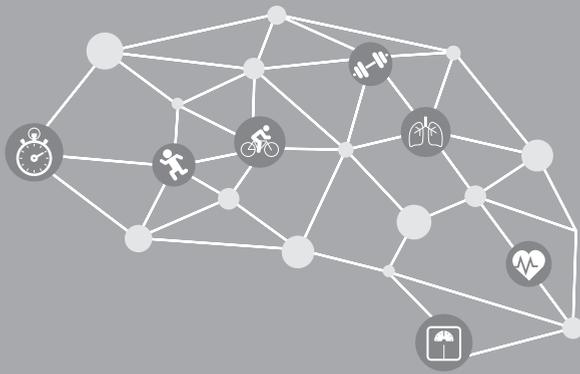
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# CHAPTER 3

**Impaired muscle strength may  
contribute to fatigue in patients with  
aneurysmal subarachnoid hemorrhage**

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**ABSTRACT**

Patients with aneurysmal subarachnoid hemorrhage (a-SAH) show long-term fatigue and have difficulties with resuming daily physical activities. Impaired muscle strength, especially in the lower-extremity, impacts the performance of daily activities and may trigger the onset of fatigue complaints. The present study evaluated maximal isokinetic knee muscle strength and fatigue in patients with a-SAH at six months post onset. Thirty-three patients and 33 sex- and age-matched healthy controls participated. Isokinetic muscle strength of the knee extensors and flexors was measured at 60°/s and 180°/s. Maximal voluntary muscle strength was defined as peak torque and measured in newton-meter. Fatigue was examined using the Fatigue Severity Scale (FSS). In patients with a-SAH, maximal knee extension was 22% (60°/s) and 25% (180°/s) lower and maximal knee flexion 33% (60°/s) and 36% (180°/s) lower compared to that of controls ( $p \leq 0.001$ ). Further, the FSS-score was related to maximal isokinetic knee extension (60°/s:  $r = -0.426$ ,  $p = 0.015$ ; 180°/s:  $r = -0.376$ ,  $p = 0.034$ ) and flexion (60°/s:  $r = -0.482$ ,  $p = 0.005$ ; 180°/s:  $r = -0.344$ ,  $p = 0.083$ ). Knee muscle strength was 28% to 47% lower in fatigued ( $n = 13$ ) and 11% to 32% lower in non-fatigued patients ( $n = 20$ ); deficits were larger in fatigued patients ( $p < 0.05$ ), particularly when the muscle strength (PT) was measured at 60°/s. Present results indicate that patients with a-SAH have considerably impaired knee muscle strength which is related to more severe fatigue. Present findings are exploratory but showed that knee muscle strength may play a role in the severity of fatigue complaints, or vice versa. Interventions targeting fatigue after a-SAH seem necessary and may consider strengthening exercise training in order to evaluate whether increased muscle strength reduces fatigue, to prevent debilitating conditions in a-SAH.

## INTRODUCTION

Aneurysmal subarachnoid hemorrhage (a-SAH) is caused by spontaneous rupture of an intracranial aneurysm.<sup>1</sup> Advances in diagnostic and therapeutic options have gradually increased survival rates up to 65%.<sup>2</sup> Those who survive experience long-term symptoms, such as cognitive impairment (40%) and fatigue (31 to 91%).<sup>3-5</sup> These long term sequelae seem to impact the reintegration into society.<sup>6</sup> Only one-third is able to fully resume their previous occupation, and half of the patients have difficulties with resuming daily activities.<sup>7,8</sup>

Muscle strength is a key-component of physical fitness and refers to the ability of a muscle group to exert force.<sup>9</sup> Loss of muscle strength, especially in the lower-extremity, impacts the performance of daily activities and may trigger the onset of fatigue complaints.<sup>10-12</sup> Muscle strength of the knee extensors and flexors is found to be an important predictor of independent daily functioning in different patient groups, including stroke.<sup>13,14</sup>

In patients with stroke, not caused by a-SAH, impaired knee muscle strength is a well-known deficit. Knee muscle strength was found to be 17% to 75% lower compared to controls, and exercise training has become an integral component of rehabilitation.<sup>15,16</sup> Exercise interventions in stroke rehabilitation are found to increase functional outcome, physical activity and quality of life.<sup>17-20</sup>

Patients with a-SAH have few, if any, neuro-motor problems and seem to have a better functional outcome than patients with other types of stroke.<sup>21</sup> Therefore, muscle strength deficits may not necessarily appear in these patients. However, fatigue complaints are highly present in a-SAH, and could easily lead to a vicious circle of physical deconditioning, in which fatigue leads to the avoidance of physical activities with subsequent reductions in muscle strength. This vicious circle is found to introduce adverse health consequences in patients with chronic conditions and seems to impact daily functioning.<sup>10,22</sup> However, muscle strength has not yet been studied in a-SAH. Knowledge about muscle strength gives insights into the physical abilities of these patients and may help to better understand a-SAH related consequences. Furthermore, by exploring relationships between fatigue and muscle strength we may optimize recommendations and provide implications for treatment.

In this study we investigated the maximal isokinetic knee extensor and flexor strength in patients with a-SAH. The knee muscle strength of patients was compared to that of sex- and age-matched healthy controls. In addition, relationships between the knee muscle strength and severity of fatigue were explored. Further, we determined knee

muscle strength in fatigued and non-fatigued patients. We hypothesized that knee muscle strength is impaired after a-SAH and considerably more impaired in fatigued than in non-fatigued patients.

## **METHODS**

The present study, 'HIPS-Rehab', is part of the prospective observational study; Hypopituitarism In Patients after Subarachnoid hemorrhage study (HIPS).<sup>23</sup> HIPS-Rehab focusses on a-SAH related consequences from a rehabilitation perspective and includes measurements on physical fitness. In the present study we describe data on muscle strength and fatigue in patients who were six months post a-SAH. The study was approved by the Medical Ethics Committee of the Erasmus University Medical Centre, and all participants provided written informed consent.

### **Procedures and participants**

All patients with a-SAH included in the HIPS-study aged  $\geq 18$  years, were discharged from the intensive care unit (ICU) and treated by Department of Neurology of the Erasmus Medical Centre between June 2009 and June 2012. A diagnosis of a-SAH was confirmed by computed tomography (CT) of the brain or lumbar puncture. The presence and location of aneurysms were determined by CT angiography or digital subtraction angiography. Patients were excluded if they met any of the following criteria: SAH of non-aneurysmal origin; hypothalamic or pituitary disease diagnosed prior to a-SAH; history of cranial irradiation; trauma capitis prior to a-SAH; a history of any prior intracranial lesion; or other medical or psychiatric conditions or laboratory abnormalities that could interfere with the outcome of the study. Additional exclusion criteria for HIPS-Rehab were: not eligible to perform maximal exercise testing, as indicated by treating physician using the Physical Activity Readiness Questionnaire (PAR-Q)<sup>24</sup> and a medical history questionnaire (developed for this study and available on request); or aged  $\geq 70$  years. All patients were screened for growth hormone (GH)-deficiency because this may be a result of post a-SAH hypopituitarism and found to be related to both fatigue and muscle strength.<sup>25,26</sup> GH-deficiency was defined as an insufficient GH response to a GH releasing hormone (GHRH)-arginine test.<sup>23</sup>

Since Dutch reference values for knee muscle strength are lacking, we included a comparison group of healthy controls. Controls were recruited by advertisement and were included based on sex and age ( $\pm 5$  years). Patients and controls performed identical testing protocols.

## Measures

### *Muscle strength*

Maximal isokinetic muscle strength of the knee extensors and flexors was measured using a Biodex® dynamometer (Shirley, New York, USA). Participants were seated and firmly strapped at the chest, hip and thigh. The rotational axis of the dynamometer was aligned with the lateral femoral epicondyle. Isokinetic muscle strength was measured in both legs at two different isokinetic velocities: with 5 maximal contractions at 60°/s and 15 maximal contractions at 180°/s. Muscle strength was recorded in Torque (Nm). Peak Torque (PT) was considered the maximum torque generated throughout one series of repetitions and was expressed in absolute PT (Nm) and relative PT, corrected for body mass ( $\text{Nm}\cdot\text{kg}^{-1}$ ) and fat free mass ( $\text{Nm}\cdot\text{kg FFM}^{-1}$ ). Since there were no differences in muscle strength between the left and right lower limb, we calculated the average PT of both limbs (data not presented). Isokinetic velocities were chosen for consistency with other studies, including studies on patients with stroke.<sup>13, 15, 16, 27</sup>

Fatigue was assessed using the Dutch version of the Fatigue Severity Scale (FSS).<sup>28</sup> The FSS is a nine-item validated questionnaire assessing the impact of fatigue on daily functioning,<sup>29</sup> with higher FSS-scores indicating more severe fatigue. The mean score of the nine items ranges from 1 ('no signs of fatigue') to 7 ('most disabling fatigue'). Fatigue was defined as a score of more than 1 SD above the mean for healthy individuals (mean FSS-score  $\geq 4.0$ ).<sup>29</sup> The FSS is widely used and has shown validity in several patient groups, including patients with stroke.<sup>30, 31</sup>

### *Clinical and personal characteristics*

The following clinical characteristics were collected: location of the aneurysm (anterior or posterior circulation); treatment modality (surgical clipping or endovascular coiling); severity of a-SAH, as determined by the World Federation of Neurologic Surgeons (WFNS)-grade and Glasgow Coma Scale (GCS)-score;<sup>32</sup> the occurrence of secondary health complications (re-bleeding of the aneurysm, hyponatremia, hydrocephalus and growth hormone deficiency), and neurological morbidity (paresis or spasticity).

Additionally, we examined body composition in patients and controls. Body mass index (BMI) was calculated from height and body mass ( $\text{kg}/\text{m}^2$ ); waist circumference (cm) was measured midway between the lowest rib and the iliac crest while standing; thickness of four skinfolds (biceps, triceps, subscapular, and supra-iliac region) was measured twice at the left side of the body with a Harpenden Skinfolds Caliper (Burgess Hill, UK); mean of two measurements was used to predict percentage body fat from which we calculated the fat free mass (FFM).<sup>33</sup>

Furthermore, questions regarding participation in sports and/or moderate intensive daily physical activities (including recreational activities such as cycling, swimming and walking) were completed.

### **Statistical analyses**

All data are expressed as mean (SD) unless otherwise indicated. To compare data of participants with non-participants (in HIPS but not in HIPS-Rehab), independent t-tests were applied for continuous data and chi-square tests were used for categorical data. To compare participants' characteristics and knee muscle strength data of patients to that of controls, paired sample t-tests were used for continuous data and chi-square for categorical data. Pearson's correlation coefficients were calculated to investigate relationships between the knee muscle strength and FSS-score. Further, we explored muscle strength in fatigued (mean FSS-score $\geq$ 4.0) and non-fatigued patients (mean FSS-score $<$ 4.0). Deficits in muscle strength were calculated using the following formula:

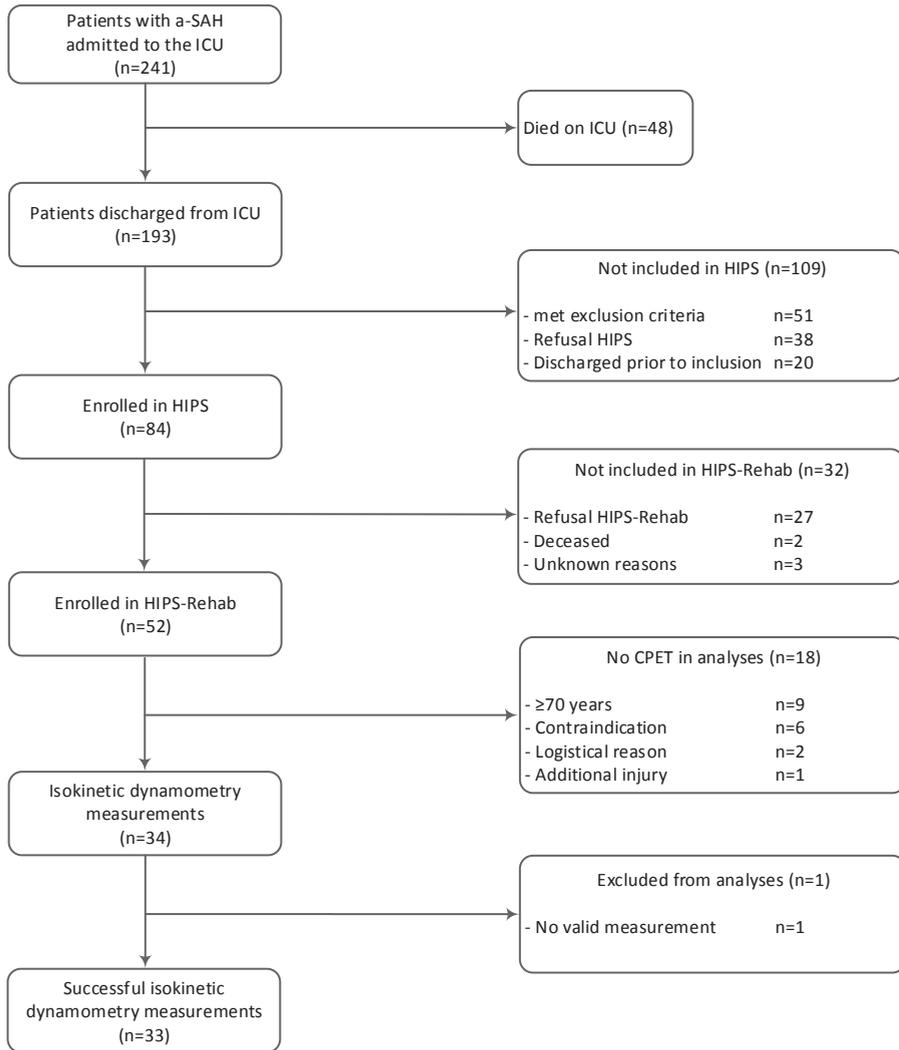
$$\frac{PT\ patient - PT\ control}{PT\ control} * 100\%$$

To compare deficits between fatigued and non-fatigued patients, we used an independent t-test. A probability value of  $p < 0.05$  was considered statistically significant. To adjust for multiplicity, we applied a Bonferroni correction. Statistical analyses were performed using IBM SPSS Statistics 20 (SPSS Inc., Chicago, IL, USA).

## **RESULTS**

Between June 2009 and June 2012, 241 patients were admitted to the ICU with a diagnosis of a-SAH of which 52 participated in HIPS-Rehab. In total, 34 patients (65%) completed measurements of muscle strength and fatigue. Because one patient could not adequately perform isokinetic muscle strength measurement, 33 measurements were analyzed. A consort flow diagram is presented in Figure 1.

Patients' characteristics are presented in Table 1. Except that patients were younger (mean difference 10.0 (SD 3.0) years;  $p = 0.002$ ), they did not differ from those who were excluded from the final analyses ( $n = 19$ ). The neurological scores showed that 78% of the patients had a low-grade a-SAH and a mean GCS-score of 13.7 (SD 2.1). Most patients underwent endovascular coiling (85%) and four patients had a GH-deficiency (12%). None of the patients had a paresis or showed signs of spasticity. All patients were discharged to their home environment.



**Figure 1.** Consort flow diagram.

Characteristics of patients and controls are presented in Table 2. Patients had significantly higher BMI and waist circumference (95% CI of the difference: 1.7 to 4.4;  $p < 0.001$ ). Furthermore, patients participated less in sports and/or moderate intensive daily physical activities than controls (45% vs. 91%, respectively;  $\chi^2 = 15.71$ ;  $p < 0.001$ ). Fatigue was more prevalent in patients, being present in 13 patients and two controls ( $\chi^2 = 10.44$ ;  $p = 0.001$ ).

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**Table 1.** Patients' characteristics

Characteristics	Patients with a-SAH (n=33)
Age (years), mean (SD)	52.5 (9.5)
Sex, males, n (%)	10 (30)
Location of aneurysm, n (%)	
- Anterior circulation	18 (55)
- Posterior circulation	15 (45)
Aneurysmal treatment, n (%)	
- Surgical clipping	5 (15)
- Endovascular coiling	28 (85)
WFNS-grade, n (%)	
I	17 (51)
II	9 (27)
III	1 (3)
IV	5 (15)
V	1 (3)
Glasgow Coma Scale-score, mean (SD)	13.6 (2.1)
Complications, n (%)	
- Rebleeding aneurysm	0 (-)
- Delayed cerebral ischemia	7 (25)
- Hyponatremia	4 (14)
- Hydrocephalus	11 (32)
- Growth Hormone deficient	4 (12)

Note: Values are presented as n (%) or mean (SD). WFNS, World Federation of Neurologic Surgeons grading system for subarachnoid hemorrhage.

**Table 2.** Characteristics of patients and matched control subjects.

Characteristics	Patients with a-SAH (n=33)	Healthy controls (n=33)	p-value
Age (years), mean (SD)	52.5 (9.5)	51.6 (8.9)	-
Sex, males, n (%)	10 (30)	10 (30)	-
BMI (kg/m <sup>2</sup> ), mean (SD)	27.1 (3.4)	24.0 (2.1)	<0.001
Weight (kg), mean (SD)	75.9 (10.6)	72.2 (8.9)	0.101
Percentage body fat (%), mean (SD)	35.3 (7.3)	32.4 (5.8)	0.074
FFM (kg FFM), mean (SD)	48.8 (9.1)	49.1 (8.6)	0.908
Waist circumference (cm), mean (SD)	93.3 (9.3)	83.6 (8.3)	<0.001
Participation in sports, n (%)*	15 (45)	30 (91)	<0.001
<b>Fatigue</b>			
FSS-score, mean (SD)	3.5 (1.4)	2.4 (0.9)	0.001
- Non-fatigued (<4.0), n (%)	20 (61)	31 (94)	0.001
- Fatigued (≥4.0), n (%)	13 (39)	2 (6)	

Note: Values are presented as mean (SD) or n (%). a-SAH, aneurysmal subarachnoid hemorrhage; BMI, body mass index; FFM, fat-free mass; FSS-score, Fatigue Severity Scale score.

daily physical activities than controls (45% vs. 91%, respectively;  $\chi^2=15.71$ ;  $p<0.001$ ). Fatigue was more prevalent in patients; being present in 13 patients and two controls ( $\chi^2=10.44$ ;  $p=0.001$ ).

Measures of knee muscle strength were 21% to 36% lower in patients compared to matched controls. Maximal isokinetic muscle strength PT (Nm) was 21% lower for extension at 60°/s; 25% lower for extension at 180°/s; 33% lower for flexion at 60°/s and 36% lower for flexion at 180°/s ( $p<0.001$ ). Similar differences were found for knee muscle strength (PT), normalized for body mass ( $\text{Nm}\cdot\text{kg}^{-1}$ ) and fat free mass ( $\text{Nm}\cdot\text{kg FFM}^{-1}$ ) (Table 3).

Pearson's correlation coefficient showed that the FSS-score was related to PT extension 60°/s ( $r=-0.426$ ;  $p=0.015$ ), PT extension 180°/s ( $r=-0.376$ ;  $p=0.034$ ), PT flexion 60°/s ( $r=-0.482$ ;  $p=0.005$ ) and PT flexion 180°/s ( $r=-0.344$ ;  $p=0.083$ ). Similar correlation coefficients were found between FSS-score and PT normalized for body mass ( $\text{Nm}\cdot\text{kg}^{-1}$ ) (PT extension 60°/s:  $r=-0.393$ ;  $p=0.026$ ; PT extension 180°/s:  $r=-0.309$ ;  $p=0.086$ ; PT flexion 60°/s:  $r=-0.427$ ;  $p=0.015$ ; PT flexion 180°/s:  $r=-0.350$ ;  $p=0.049$ ) and fat free mass ( $\text{Nm}\cdot\text{kg FFM}^{-1}$ ) (PT extension 60°/s:  $r=-0.429$ ;  $p=0.014$ ; PT extension 180°/s:  $r=-0.357$ ;  $p=0.045$ ; PT flexion 60°/s:  $r=-0.432$ ;  $p=0.014$ ; PT flexion 180°/s:  $r=-0.255$ ;  $p=0.167$ ).

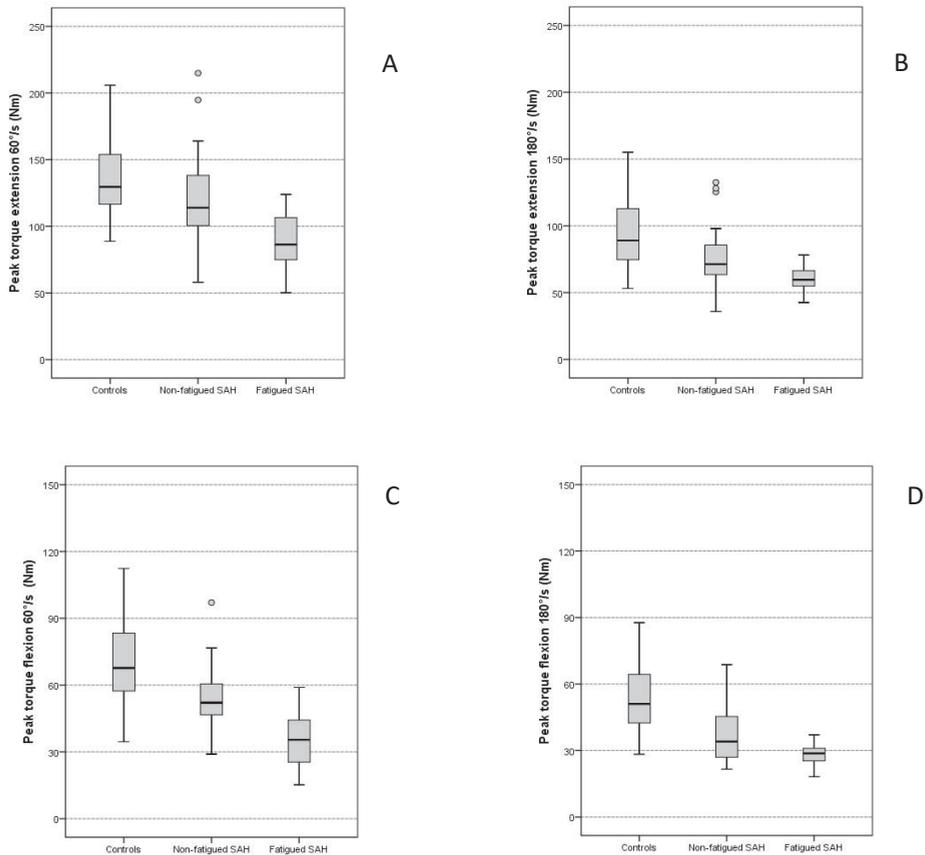
**Table 3.** Muscle strength of patients and matched controls.

Muscle strength	Patients with a-SAH (n=33)	Healthy controls (n=33)	95% CI of the difference	p-value
PT (Nm), mean (SD)				
Extension 60°/s	107.6 (36.5)	137.5 (30.0)	-46.3 to -13.4	0.001 <sup>†</sup>
Extension 180°/s	70.3 (23.0)	94.1 (24.6)	-35.5 to -12.1	<0.001 <sup>†</sup>
Flexion 60°/s	46.9 (17.8)	70.5 (18.5)	-32.5 to -14.6	<0.001 <sup>†</sup>
Flexion 180°/s	34.4 (11.8)	53.6 (14.6)	-25.8 to -12.4	<0.001 <sup>†</sup>
PT ( $\text{Nm}\cdot\text{kg}^{-1}$ ), mean (SD)				
Extension 60°/s	1.42 (0.39)	1.90 (0.33)	-0.7 to -0.3	<0.001 <sup>†</sup>
Extension 180°/s	0.93 (0.25)	1.29 (0.27)	-0.5 to -0.2	<0.001 <sup>†</sup>
Flexion 60°/s	0.62 (0.22)	0.98 (0.22)	-0.5 to -0.2	<0.001 <sup>†</sup>
Flexion 180°/s	0.44 (0.16)	0.74 (0.17)	-0.4 to -0.2	<0.001 <sup>†</sup>
PT ( $\text{Nm}\cdot\text{kg FFM}^{-1}$ ), mean (SD)				
Extension 60°/s	2.19 (0.53)	2.76 (0.34)	-0.8 to -0.3	<0.001 <sup>†</sup>
Extension 180°/s	1.44 (0.33)	1.87 (0.24)	-0.6 to -0.3	<0.001 <sup>†</sup>
Flexion 60°/s	0.96 (0.31)	1.41 (0.23)	-0.6 to -0.3	<0.001 <sup>†</sup>
Flexion 180°/s	0.70 (0.20)	1.07 (0.16)	-0.5 to -0.3	<0.001 <sup>†</sup>

Abbreviations: a-SAH, aneurysmal subarachnoid hemorrhage; PT, Peak Torque; FFM, fat-free mass.

<sup>†</sup>Significant after Bonferroni correction adjusting for multiplicity:  $p=0.05/12=0.004$

According to the FSS-score, 13 patients were fatigued (39%, mean FSS-score $\geq$ 4.0) and 20 non-fatigued (61%, mean FSS-score $<$ 4.0). There were no differences in clinical characteristics between fatigued and non-fatigued patients. One patient with GH-deficiency was fatigued. Independent t-test showed that muscle strength of the knee extensors and flexors were lower in both fatigued and non-fatigued patients compared to matched controls. These differences remained significant after correcting PT for body mass ( $\text{Nm}\cdot\text{kg}^{-1}$ ) and fat free mass ( $\text{Nm}\cdot\text{kg FFM}^{-1}$ ). Compared with controls, muscle strength was 28% to 47% lower in fatigued patients and 11% to 32% in non-fatigued patients; deficits were larger in fatigued patients, particularly when muscle strength was measured at an isokinetic velocity rate of  $60^\circ/\text{s}$  ( $p<0.05$ ). (Table 4) Figure 2 shows a graphic representation of the absolute PTs in controls, non-fatigued and fatigued patients.



**Figure 2.** Knee muscle strength in controls, non-fatigued and fatigued patients with a-SAH. Boxplots for: (A) Peak torque extension  $60^\circ/\text{s}$ , (B) Peak torque extension  $180^\circ/\text{s}$ , (C) Peak torque flexion  $60^\circ/\text{s}$  and (D) Peak torque flexion  $180^\circ/\text{s}$ , percentiles are 90<sup>th</sup>, 75<sup>th</sup>, 50<sup>th</sup>, 25<sup>th</sup> and 10<sup>th</sup>.

**Table 4.** Muscle strength in fatigued and non-fatigued patients as a percentage of matched controls.

Muscle Strength	Fatigued a-SAH (n=13)	Deficit (%) <sup>#</sup>	Non-fatigued a-SAH (n=20)	Deficit (%) <sup>#</sup>	95% CI difference in deficit	p-value <sup>§</sup>
PT (Nm), mean (SD)						
Extension 60°/s	87.6 (21.9)*	- 35.1% (18.1)	120.5 (38.7)	- 10.9% (23.0)	8.7 to 39.5	0.003 <sup>†</sup>
Extension 180°/s	60.2 (11.2)*	- 31.4% (19.6)	76.9 (26.5)*	- 17.7% (24.1)	-2.5 to 30.1	0.095
Flexion 60°/s	35.3 (12.8)*	- 43.0% (24.1)	54.5 (16.8)*	- 22.0% (25.2)	3.0 to 38.9	0.024
Flexion 180°/s	26.3 (39.2)*	- 41.6% (12.8)	38.1 (13.1)*	- 26.8% (30.5)	-4.1 to 33.9	0.121
PT (Nm·kg <sup>-1</sup> ), mean (SD)						
Extension 60°/s	1.22 (0.21)*	- 36.0% (13.2)	1.54 (0.43)*	- 16.8% (21.9)	5.4 to 33.0	0.008
Extension 180°/s	0.85 (0.13)*	- 32.7% (11.9)	0.98 (0.29)*	- 23.3% (20.4)	-5.0 to 21.9	0.210
Flexion 60°/s	0.49 (0.15)*	- 43.9% (24.0)	0.70 (0.22)*	- 26.2% (26.0)	0.6 to 36.1	0.058
Flexion 180°/s	0.37 (0.12)*	- 46.5% (20.6)	0.49 (0.16)*	- 31.7% (26.5)	-2.9 to 32.5	0.095
PT (Nm·kg FFM <sup>-1</sup> ), mean (SD)						
Extension 60°/s	1.95 (0.43)*	- 31.4% (17.3)	2.35 (0.54)*	- 12.6% (22.1)	3.8 to 33.7	0.016
Extension 180°/s	1.34 (0.23)*	- 27.8% (17.1)	1.50 (0.38)*	- 19.4% (19.0)	-5.0 to 21.9	0.210
Flexion 60°/s	0.79 (0.28)*	- 40.3% (24.7)	1.08 (0.28)*	- 21.2% (23.2)	1.6 to 36.6	0.033
Flexion 180°/s	0.63 (0.10)*	- 39.3% (13.9)	0.75 (0.21)*	- 27.6% (23.4)	-3.6 to 27.0	0.130

$$\# \text{ Deficit} = \frac{PT \text{ patient} - PT \text{ control}}{PT \text{ control}} * 100\%;$$

\* PT significantly lower compared to matched controls after Bonferroni correction adjusting for multiplicity: p=0.05/12=0.004;

<sup>†</sup> Deficit significantly different after Bonferroni correction adjusting for multiplicity: p=0.05/12=0.004;

<sup>§</sup> Difference in deficit (%) between fatigued and non-fatigued patients.

## DISCUSSION

This study shows that knee muscle strength was considerably lower in patients with a-SAH compared to that of matched controls. Measures of knee muscle strength were found to be 21% to 36% lower in patients than in controls. Further, we found significant relationships between the knee muscle strength and the severity of fatigue. In comparison with controls, deficits in knee muscle strength ranged from 28% to 47% in fatigued patients, whereas these ranged from 11% to 32% in non-fatigued patients. The results indicate that deficits in muscle strength may play a role in fatigue, or vice versa. Impaired muscle strength can be debilitating as it affects activities of daily living. Present findings are exploratory but indicate that patients with a-SAH, and particularly those who are fatigued, have impaired knee muscle strength which may hold implication for treatment. Interventions seem necessary and should take into account physical deconditioning and a potential loss of knee muscle strength.

In non-a-SAH stroke patients, deficits in muscle strength range from 17% to 75%.<sup>15, 16</sup> In these patients, impaired muscle strength is largely explained by neuro-motor lesions. However, patients with a-SAH often have few, if any, neuro-motor lesions. Therefore, different mechanisms may be involved. An interesting study by Eng et al. showed that the preservation of muscle strength seems to be related to levels of physical activity after stroke.<sup>34</sup> Physical inactivity may lead to physical deconditioning and subsequent avoidance of physical demanding activities. Since fatigue is highly prevalent in a-SAH, such a negative circle of physical inactivity and physical deconditioning may also apply to patients with a-SAH.<sup>10</sup> The fact that patients participated less in sports and/or moderate intensive daily physical activities may indicate that patients with a-SAH are less physically active.

Hypopituitarism with GH-deficiency has been reported frequently in patients with a-SAH and is found to be associated with both fatigue and lower muscle strength.<sup>25, 26</sup> However, the fact that only four patients (=12%) had GH-deficiency indicates that impaired muscle strength may occur independent of GH-deficiency. One patient with GH-deficiency reported fatigue complaints. Unfortunately, the small number of GH-deficient patients did not allow for correction of GH-deficiency in the evaluation of muscle strength after a-SAH.

In total, 39% of the patients reported fatigue complaints and had considerably low knee muscle strength. Previous literature showed that improved muscle strength can provide a physical reserve to fatigue, and a margin of safety during physical demanding activities.<sup>11, 13</sup> Therefore, strengthening exercise training should be considered for patients with a-SAH. Studies in patients with non-a-SAH stroke types showed that strengthening exercise increases muscle strength and improves functional outcome.<sup>17</sup> Moreover, beneficial effects of exercise training on disease-related fatigue and emotional challenges have been reported.<sup>35, 36</sup> Accordingly, intervention studies are warranted to investigate the added value of strengthening exercise in a-SAH.

The multidimensional character of fatigue should be noted.<sup>3</sup> Sleep disturbances, anxiety, depression, posttraumatic stress and cognitive impairments have already been associated with fatigue in a-SAH.<sup>3</sup> Therefore, future interventions targeting fatigue in a-SAH, should take into account its' multidimensional character. Strengthening exercise training is unlikely to be the 'golden bullet' treating fatigue, it is rather a potential contributor in the treatment of a debilitating condition.

The inclusion of sex- and age-matched controls is a major strength of the present study, and is frequently done to examine muscle strength across different patient groups, including patients with stroke.<sup>25, 34, 37</sup>

Some possible limitations should be discussed. First, our study is limited by its cross-sectional design; therefore, we cannot infer causality from the present results. Second, selection bias may be involved in both patients and controls. Since patients were excluded when they were not eligible to perform maximal exercise testing, it is likely that we have excluded those with severely impaired knee muscle strength which may have underestimated muscle strength deficits in a-SAH. On the other hand, controls who were interested to participate are more likely to take part in sports and moderate intensive daily physical activities which may have resulted in an overestimation of the muscle strength deficits. Because there are no appropriate reference data available on participation in sports and/or moderate intensive daily physical activities for the Dutch population, we were not able to make up an appropriate comparison. However, knee muscle strength of the controls is comparable to that of Swedish reference data.<sup>38</sup> Another possible limitation is that controls were only matched based on sex and age. However, in an attempt to adjust for potential other confounders, we performed analyses on muscle strength normalized for body mass and fat free mass.

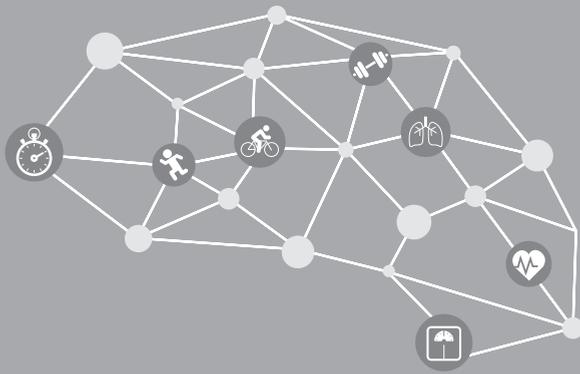
## CONCLUSIONS

We showed impaired knee muscle strength in patients with a-SAH. Interestingly, knee muscle strength was related to the severity of fatigue which indicates that knee muscle strength may play a role in fatigue, or vice versa. Although the present findings are exploratory, knee muscle strength was more impaired in fatigued patients than in non-fatigued patients, particularly when knee muscle strength was measured at a lower isokinetic velocity rate. Present findings indicate that interventions after a-SAH are necessary. Interventions targeting fatigue should take into account its' multidimensional character, in which strengthening exercise may contribute to a multimodal treatment of a debilitating condition.

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# CHAPTER 4

## Impaired cardiorespiratory fitness after aneurysmal subarachnoid hemorrhage

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## ABSTRACT

**Objective:** To assess the cardiorespiratory fitness in patients after suffering an aneurysmal subarachnoid hemorrhage and to explore this in fatigued and non-fatigued patients.

**Design:** Cross-sectional case-control study.

**Participants:** Twenty-eight patients, six months post aneurysmal subarachnoid hemorrhage, and 28 sex- and age-matched controls.

**Methods:** Cardiorespiratory responses to a progressive cardiopulmonary exercise test on a cycle ergometer were obtained using indirect calorimetry. Fatigue was assessed using the Fatigue Severity Scale.

**Results:** Peak oxygen uptake ( $\dot{V}O_{2\text{peak}}$ ) was significantly lower in patients (22.0 (SD 6.2)  $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) than in controls (69% of controls,  $p<0.001$ ). All other cardiorespiratory fitness parameters were also lower, with peak levels ranging from 62% to 77% of matched controls. Mean  $\dot{V}O_{2\text{peak}}$  was 19.4 (SD 4.1)  $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  in fatigued patients (63% of matched controls,  $p<0.001$ ) and 23.9 (SD 6.9)  $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  in non-fatigued patients (74% of matched controls,  $p=0.002$ ).

**Conclusion:** Cardiorespiratory fitness is impaired after aneurysmal subarachnoid hemorrhage, both in fatigued and non-fatigued patients. This finding may have implications for treatment.

## INTRODUCTION

Aneurysmal subarachnoid hemorrhage (a-SAH) is a potential life-threatening stroke which accounts for 5% of all stroke cases.<sup>1, 2</sup> Advances in diagnostic and surgical management have increased the chance of surviving an a-SAH, survival rates reaches 65%.<sup>3</sup> With a growing number of patients surviving, understanding the long-lasting sequelae of a-SAH becomes increasingly important.

With only one-third of the survivors being able to fully resume previous occupation, a-SAH has a significant impact on society, patients' families and of course on patients themselves.<sup>3, 4</sup> Long-term cognitive and emotional problems may be present,<sup>5</sup> and one of the most distressing complaints is fatigue which has a prevalence rate that ranges from 31% to 91%.<sup>6</sup> Fatigue may persist up to 7 years post a-SAH,<sup>7</sup> and is associated with many factors, including sleep disturbances, anxiety, emotional problems, passive coping styles, and cognitive impairment.<sup>6</sup> An interesting hypothesis is that the presence of fatigue may be a result of impaired cardiorespiratory fitness, triggered by physical deconditioning.<sup>6, 8</sup> Associations between cardiorespiratory fitness and fatigue have been found across several non-stroke patient groups.<sup>9-12</sup>

Cardiorespiratory fitness is defined as the ability of the cardiorespiratory system to supply oxygen to the skeletal muscles during sustained physical activity.<sup>13</sup> In patients with stroke, not caused by a-SAH, the cardiorespiratory fitness is almost half that of sex and age-matched controls.<sup>14</sup> In these patients, the beneficial effects of improved cardiorespiratory fitness are well-recognized, and exercise training has become an integral component of stroke rehabilitation.<sup>15</sup> Such training contributes to cardiovascular health and can provide a physical reserve to fatigue.<sup>14, 16</sup> However, to our knowledge, the cardiorespiratory fitness has not yet been studied in a-SAH, and deserves attention in rehabilitation medicine.

The primary goal of this study was to assess the cardiorespiratory fitness in patients with a-SAH, and to explore fitness levels in fatigued and non-fatigued patients. Cardiorespiratory responses to a progressive cardiopulmonary exercise test were compared to that of sex and age-matched controls. We hypothesized that cardiorespiratory fitness will be impaired in a-SAH, particularly in fatigued patients.

## METHODS

This case-control study, entitled HIPS-Rehab, was part of a longitudinal observational study, entitled: Hypopituitarism In Patients after Subarachnoid haemorrhage (HIPS).<sup>17</sup> HIPS-Rehab focuses on a-SAH related consequences from a rehabilitation perspective and includes measurements on physical fitness and physical activity. In the present study we used data measured at six months post onset. The study was approved by the Medical Ethics Committee of the Erasmus University Medical Centre, and all participants gave written informed consent.

### Procedures and participants

Patients with a-SAH admitted to the department of Neurology of the Erasmus Medical Centre, The Netherlands, between June 2009 and June 2012 were eligible for inclusion when they were discharged from the intensive care unit (ICU) and aged  $\geq 18$  years. Diagnosis of aneurysmal subarachnoid hemorrhage was confirmed by computerized tomography (CT) of the brain and in cases with negative CT, by lumbar puncture. Presence and location of the aneurysm was determined by CT angiography and/or a digital subtraction angiography. Patients were excluded if they met any of the following criteria: 1) hypothalamic or pituitary disease diagnosed prior to a-SAH; 2) history of cranial irradiation; 3) trauma capitis prior to a-SAH; 4) other intracranial lesion apart from a-SAH; or 5) other medical or psychiatric condition or laboratory abnormality that may interfere with the outcome of the study. Additional exclusion criteria regarding physical fitness measurements were: aged  $\geq 70$  years, and not eligible to perform maximal exercise testing, as indicated by treating physician and the Physical Activity Readiness Questionnaire (PAR-Q).<sup>18</sup>

Since appropriate Dutch reference values for cardiorespiratory fitness are not available, we included a comparison group. Each patient was individually paired with a control subject with respect to sex and age ( $\pm 5$  years). Controls were recruited by advertisement and screened on medical contraindications for physical exercise by a physician using the PAR-Q,<sup>18</sup> and a questionnaire concerning medical history and sports participation (developed for this study and available on request).

This is the first study to specifically investigate cardiorespiratory responses to progressive CPET in a-SAH. Therefore, we have implemented a supplementary safety protocol which matches the recommendations for conducting CPET in stroke.<sup>19</sup> First, all patients were screened for absolute and relative medical contraindications to physical exercise by a neurologist and a sports physician. If there was any suspicion of underlying cardiovascular or pulmonary pathology, progressive CPET was not carried out. In addition, resting

blood pressure was recorded twice prior to CPET with a few minutes of rest between measurements. During CPET, blood pressure was measured using an automatic system, heart function was monitored using a 12-lead electrocardiogram and a sports physician served as emergency back-up.

## Outcome measures

### *Cardiorespiratory fitness*

CPET was performed using a progressive ramp protocol on an electronically braked cycle ergometer (Jaeger ER800, Toennies, Breda, The Netherlands). This method of testing has been frequently applied after stroke, and is feasible in a selected group of stroke patients who underwent pre-test medical screening.<sup>19</sup> Gas exchange analyses were performed during CPET by indirect calorimetry using the Oxycon Pro (CareFusion, Houten, The Netherlands), a breath-by-breath oximetry analysing system.

Participants were instructed to abstain from consuming food or caffeine prior to CPET. Before each measurement, volume and gas calibrations were performed. After calibrations, participants warmed up for 4 minutes without resistance, after which a ramp protocol was implemented with the goal of having the participants reach their maximum physical effort within 10 to 14 minutes. Resistance increased automatically every 10 seconds and varied by sex (female: 12W/min, male: 16W/min). Participants were instructed to pedal at a rate of 60 to 70 revolutions per minute. Strong verbal encouragement was provided, to continue as long as possible until maximal voluntary exhaustion. CPET was terminated when participants reached volitional fatigue, or if they were unable to maintain target pedal rate. CPET could also be terminated because of medical complications, as prescribed in the guidelines of the ACSM for exercise testing (e.g. sustained ventricular tachycardia, ST elevation, moderately severe angina, drop in systolic blood pressure of >10 mmHg from baseline blood pressure).<sup>13</sup>

The following peak cardiorespiratory responses were analysed: oxygen consumption ( $\dot{V}O_{2\text{peak}}$ ), the criterion standard for cardiorespiratory fitness, which was expressed in absolute  $\dot{V}O_{2\text{peak}}$  ( $\text{mL}\cdot\text{min}^{-1}$ ) and relative  $\dot{V}O_{2\text{peak}}$  per kilogram body mass ( $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) and per kilogram fat-free mass ( $\text{mL}\cdot\text{kg FFM}^{-1}\cdot\text{min}^{-1}$ ); ventilation ( $\dot{V}E_{\text{peak}}$ ), a measure of pulmonary capacity ( $\text{L}\cdot\text{min}^{-1}$ ); oxygen pulse ( $\dot{V}O_{2\text{peak}}/\text{HR}_{\text{peak}}$ ), a measure of cardiac output (mL per beat); heart rate (HR) in beats per minute; respiratory rate (RR) in breaths per minute; respiratory exchange ratio (RER) ( $\dot{V}CO_2/\dot{V}O_2$ ); and the ventilatory equivalent for oxygen ( $\dot{V}E_{\text{peak}}/\dot{V}O_{2\text{peak}}$ ), a measure of ventilatory efficiency ( $\text{L}\cdot\text{min}^{-1}$ ). Cardiorespiratory responses were analysed at peak physical work rates, defined as the highest mean values recorded during 30 seconds of exercise.

Additionally, the ventilatory anaerobic threshold was estimated by two assessors using the ventilatory equivalent method;<sup>20</sup> defined as the moment at which the ventilatory equivalent for CO<sub>2</sub> (VE/VCO<sub>2</sub>) and end-tidal CO<sub>2</sub> partial pressure (PETCO<sub>2</sub>) remained stable, and the VE/VO<sub>2</sub> and the end-tidal O<sub>2</sub> partial pressure (PETO<sub>2</sub>) increased disproportionately.

Only data of participants that met at least one of the objective criteria for maximal physical exertion were included in the final analyses. The following criteria were used to determine maximal physical exertion: [1] RER of >1.0<sup>19</sup> or [2] HR<sub>peak</sub> within 10 beats per minute (bpm) of the age predicted maximum heart (HR<sub>max</sub>) rate calculated from the formula of Tanaka et al.<sup>21</sup>:

$$HR_{\max} = 208 - (0.7 * \text{age})$$

As beta-blocker medication reduces maximal heart rate by 25-30%,<sup>22</sup> the equation was adjusted for patients with beta-blocker medication:

$$HR_{\max} = 0.70 * [208 - (0.7 * \text{age})]$$

### *Fatigue*

Fatigue was measured using the Fatigue Severity Scale (FSS).<sup>23</sup> The FSS is a brief and simple instrument consisting of 9 statements about fatigue, scored on a 7-point scale ranging from 1 (strongly disagree) to 7 (strongly agree). The total score is the mean of the 9 item scores. Higher scores indicate more impact of fatigue on daily life. Fatigue was defined as a score of more than 1 standard deviation (SD) above the mean score for healthy individuals (FSS-score  $\geq 4.0$ ).<sup>24</sup> The FSS is a widely used measure of fatigue and has been validated for stroke patients in a large Swiss cohort.<sup>25</sup>

### *Clinical and personal characteristics*

The following patients' characteristics were collected: severity of a-SAH, as determined by the World Federation of Neurologic Surgeons (WFNS)-grade (low-grade: I-III or high-grade: IV-V)<sup>26</sup> and the Glasgow Coma Scale (GCS)-score;<sup>27</sup> location of the aneurysm (anterior or posterior circulation); treatment procedure (surgical clipping or endovascular treatment); neurological comorbidities (paresis or spasticity); presence of secondary complications (re-bleed, delayed cerebral ischemia, hyponatremia, hydrocephalus, and growth hormone (GH) deficiency). GH-deficiency was defined as an insufficient GH response to a GH-releasing hormone (GHRH-arginine test).<sup>17</sup> In addition, we collected data on follow-up care (i.e. discharge to the patients' home environment, a SAH outpatient aftercare clinic, or an inpatient rehabilitation center).

Body anthropometry was examined in both patients and controls: Body Mass Index (BMI) was calculated from height and body mass ( $\text{kg}/\text{m}^2$ ); waist circumference (cm) was measured midway between the lowest rib and the iliac crest while standing; thickness of four skinfolds (biceps, triceps, subscapular, and supra-iliac region) was measured twice at the left side of the body with a Harpenden Skinfolds Caliper (Burgess Hill, UK). The mean of two measurements was used to predict percentage body fat from which the fat free mass (FFM) was calculated.<sup>28</sup>

Furthermore, a questionnaire regarding participation in sports and/or moderate intensive daily physical activities (including recreational activities such as cycling, swimming and walking) was completed (developed for this study and available on request).

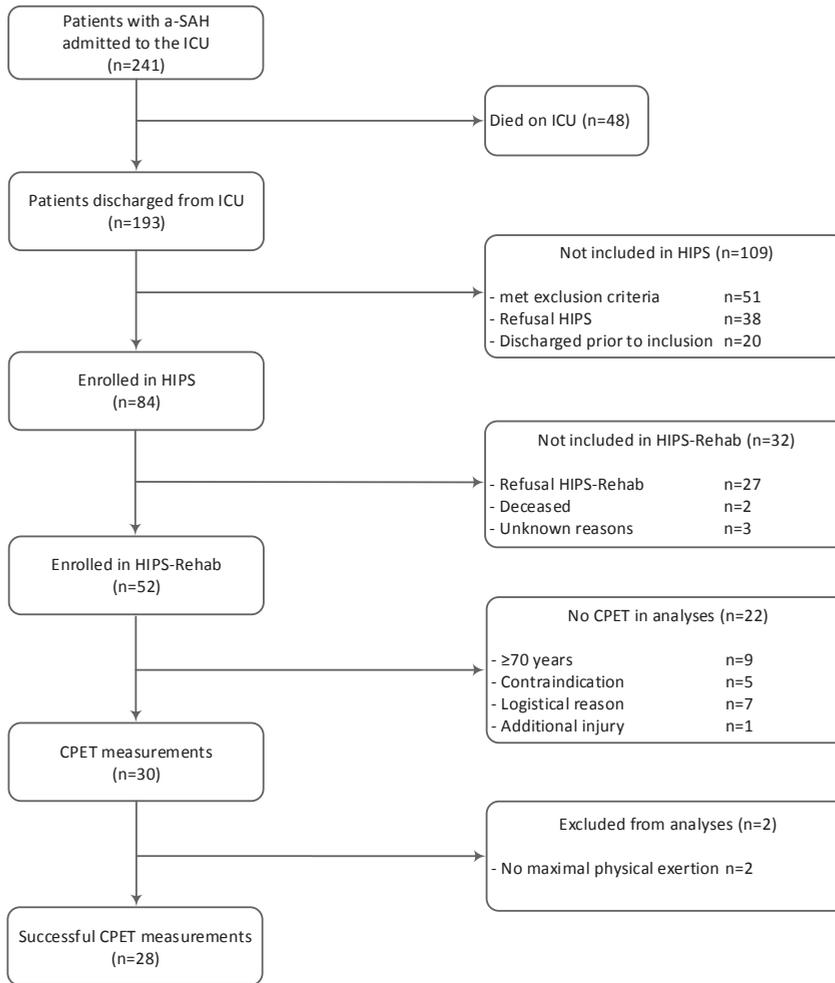
### Statistical analyses

All data are expressed as mean (SD) unless otherwise indicated. To compare data of participants with non-participants, independent t-tests were used for continuous data and chi-square tests were used for categorical data. To compare participants' characteristics and CPET data of patients to that of control subjects, paired sample t-tests were applied for continuous data, chi-square tests for categorical data. Secondary, CPET data in fatigued (FSS-score $\geq$ 4.0) and non-fatigued patients (FSS-score $<$ 4.0) were explored with descriptive statistics and compared to that of controls using paired samples t-tests. A probability value of  $p < 0.05$  was considered statistically significant. To adjust for multiplicity, we applied a Bonferroni correction. All analyses were performed using IBM SPSS Statistics, version 20 (SPSS Inc., Chicago, IL, USA).

## RESULTS

Of the 241 patients admitted to the ICU with a diagnosis of a-SAH, 84 were included in the HIPS of which 52 volunteered to participate in the HIPS-Rehab (Figure 1 presents a flow diagram). Patients in the HIPS-Rehab ( $n=52$ ) did not differ from non-participants ( $n=32$ ) with respect to the severity of a-SAH, location of the aneurysm, treatment procedure, and the presence of secondary health complications (data not presented)

Of the 52 patients in the HIPS-Rehab, 28 performed successful CPET measurements. Table 1 presents patients' characteristics. The neurological scores showed that 23 patients had a low-grade a-SAH (82%) and mean GCS-score was 13.6 (SD 2.1). The majority suffered from a ruptured aneurysm in the anterior circulation (64%) and most underwent endovascular coiling (79%). None of the patients had a paresis or showed signs of spasticity. All were discharged to their home environment, and eleven were



**Figure 1.** Consort flow diagram

redirected to an outpatient aftercare clinic (including a visit to the rehabilitation specialist, neuropsychologist and specialized nurse). Nine of the 28 patients had beta-blocker medication. According to the medical pre-screening procedure, there were no other cardiovascular or pulmonary pathologies detected. Except that the included patients were younger (mean difference 7.8 (SD 3.0) years;  $p=0.012$ ), they did not differ from those who were excluded ( $n=24$ ) from the final analyses.

Characteristics of patients and controls are presented in Table 2. BMI and waist circumference were higher in patients than in controls. Patients participated less in sports and/or in moderate intensive daily physical activities than controls (43% vs. 96%, respectively;

**Table 1.** Descriptive characteristics of the patients with a-SAH.

Characteristics	Patients with a-SAH (n=28)
Age (years), mean (SD)	53 (10)
Sex, males n (%)	8 (29)
WFNS grade, n (%)	
I	14 (50)
II	9 (32)
III	0 (-)
IV	4 (14)
V	1 (4)
Glasgow Coma Scale-score (range)	13.6 (5-15)
Location of aneurysm, n (%)	
- Anterior circulation	18 (64)
- Posterior circulation	10 (36)
Treatment procedure, n (%)	
- Surgical clipping	6 (21)
- Endovascular coiling	22 (79)
Complications, n (%)	
- Rebleed	0 (-)
- Delayed cerebral ischemia	7 (25)
- Hyponatremia	4 (14)
- Hydrocephalus	9 (32)
- Growth hormone deficient	2 (7)

Abbreviations: a-SAH, aneurysmal subarachnoid hemorrhage; WFNS, World Federation of Neurologic Surgeons grading system for subarachnoid hemorrhage.

**Table 2.** Characteristics of patients with a-SAH and of control subjects.

Characteristics	Patients with a-SAH (n=28)	Healthy controls (n=28)	95% CI for the difference	p-value
Age (years), mean (SD)	53 (9)	52 (9)	-	-
Sex, males, n (%)	8 (29)	8 (29)	-	-
Weight (kg), mean (SD)	74.5 (10.2)	72.2 (9.1)	-2.9 to 7.5	0.367
BMI (kg/m <sup>2</sup> ), mean (SD)	27.1 (3.5)	24.1 (2.1)	1.3 to 4.8	0.001
Percentage body fat (%), mean (SD)	35.3 (6.9)	32.7 (6.0)	-0.76 to 5.0	0.067
Waist circumference (cm), mean (SD)	92.5 (8.5)	83.2 (8.3)	5.1 to 13.4	<0.001
Fat free mass (kg), mean (SD)	48.1 (8.0)	48.9 (8.8)	-4.6 to 2.2	0.475
Participation in Sports, n (%) <sup>#</sup>	12 (43)	27 (96)	-	<0.001
FSS-score, mean (SD)	3.5 (1.5)	2.5 (1.0)	0.34 to 1.7	0.005
- Non-fatigued (<4.0), n (%)	16 (57)	26 (93)	-	0.002
- Fatigued (≥4.0), n (%)	12 (43)	2 (7)		

Abbreviations: a-SAH, aneurysmal subarachnoid hemorrhage; FSS-score, Fatigue Severity Scale score.

<sup>#</sup>Participation in sports and/or moderate intensive physical activities (such as cycling, swimming and walking) at least once a month.

$\chi^2=19.0$ ;  $p<0.001$ ). Furthermore, fatigue was more frequently present in patients than in controls ( $\chi^2=9.54$ ;  $p=0.002$ ).

### Cardiorespiratory fitness

Table 3 presents CPET outcome of patients and controls. All CPET measurements were terminated because of volitional fatigue; no adverse medical complications were observed. Fifteen patients (54%) terminated the test because of dyspnea and thirteen (46%) because of muscular fatigue, in controls this was nineteen (68%) and eleven (32%), respectively. Patients had a mean  $\dot{V}O_{2peak}$  of 22.0 (SD 6.2)  $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  which was 69% of that in controls ( $p<0.001$ ). All other cardiorespiratory responses, except  $VE_{peak}/\dot{V}O_{2peak}$ , were lower in patients than in controls (Table 3). CPET measurements showed that patients had a mean  $HR_{peak}$  of 154 (SD 22) which reflected 90% of predicted  $HR_{max}$ . Mean  $RER_{peak}$  was 1.14 (SD 0.08). Although patients exercised towards acceptable cardiorespiratory limits, peak values in patients were lower than in controls,  $HR_{peak}=165$  (SD 14);  $RER_{peak}=1.22$  (SD 0.08) ( $p=0.020$  and  $p<0.001$ , respectively).

**Table 3.** Cardiorespiratory fitness in patients with a-SAH and control subjects.

Cardiorespiratory fitness mean (SD)	Patients with a-SAH (n=28)	Healthy controls (n=28)	95% CI for the difference	p-value
$\dot{V}O_{2peak}$ ( $\text{mL}\cdot\text{min}^{-1}$ )	1636 (514)	2285 (561)	-910.6 to -386.4	<0.001 <sup>†</sup>
$\dot{V}O_{2peak}$ ( $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ )	22.0 (6.2)	31.5 (6.2)	-12.4 to -6.7	<0.001 <sup>†</sup>
$\dot{V}O_{2peak}$ ( $\text{mL}\cdot\text{kg FFM}^{-1}\cdot\text{min}^{-1}$ )	34.0 (8.7)	45.9 (5.9)	-15.5 to -8.3	<0.001 <sup>†</sup>
$VE_{peak}$ ( $\text{L}\cdot\text{min}^{-1}$ )	68.9 (24.7)	90.1 (25.0)	-33.8 to -9.4	0.001 <sup>†</sup>
$\dot{V}O_{2peak}/HR_{peak}$ ( $\text{mL}/\text{beat}$ )	10.9 (2.5)	13.9 (3.3)	-3.8 to -1.4	<0.001 <sup>†</sup>
$PO_{peak}$ (Watt)	130.7 (45.3)	208.7 (55.0)	-102.3 to -53.6	<0.001 <sup>†</sup>
$VE_{peak}/\dot{V}O_{2peak}$ ( $\text{L}\cdot\text{min}^{-1}$ )	42.1 (6.3)	39.2 (5.3)	-0.02 to 5.8	0.052
VAT ( $\dot{V}O_2$ ) <sup>#</sup>	15.2 (3.9)	25.7 (8.2)	-14.7 to -6.4	<0.001 <sup>†</sup>
VAT ( $\% \dot{V}O_{2peak}$ ) <sup>#</sup>	69.0 (7.8)	79.3 (7.5)	-16.2 to -4.0	0.002 <sup>†</sup>
PO on VAT (Watt) <sup>#</sup>	79.0 (29.6)	150.7 (53.7)	-99.6 to -45.3	<0.001 <sup>†</sup>
$RR_{peak}$ ( $\text{Breaths}\cdot\text{min}^{-1}$ )	36.5 (8.1)	36.8 (8.0)	-4.8 to 4.1	0.872
$HR_{peak}$ (bpm)	154 (22)	165 (14)	-20.8 to -2.0	0.020
$RER_{peak}$ ( $VCO_2/\dot{V}O_2$ )	1.14 (0.08)	1.22 (0.08)	-0.12 to -0.04	<0.001 <sup>†</sup>
$HR_{peak}$ % of $HR_{max}$	90 (12)	96 (7)	-11.7 to -1.2	0.018

Abbreviations: a-SAH, aneurysmal subarachnoid hemorrhage;  $\dot{V}O_{2peak}$ , peak oxygen consumption;  $VE_{peak}$ , peak minute ventilation;  $\dot{V}O_{2peak}/HR_{peak}$ , peak oxygen pulse;  $VCO_2$ , carbon dioxide consumption; RER, respiratory exchange ratio; PO, power output; VAT, ventilatory anaerobic threshold;  $HR_{peak}$ , peak heart rate RR, respiratory rate.

<sup>#</sup>The ventilatory anaerobic threshold could be determined in 23 patients and was compared with their matched controls (n=23);

<sup>†</sup>Significantly different after Bonferroni correction adjusting for multiplicity:  $p=0.05/14=0.004$ .

### Cardiorespiratory fitness and fatigue

Table 4 presents CPET outcome of fatigued and non-fatigued patients, and control subjects. In non-fatigued patients, nine patients (56%) terminated the test because of dyspnea and seven (44%) because of muscular fatigue. In fatigued patients, half of the patients (n=6) terminated the test because of dyspnea and the other half because of muscular fatigue. Fatigued patients had a mean  $\dot{V}O_{2\text{peak}}$  of 19.4 (SD 4.1) mL·kg<sup>-1</sup>·min<sup>-1</sup> (63% of matched controls, p<0.001) and non-fatigued patients had a mean  $\dot{V}O_{2\text{peak}}$  of 23.9 (SD 6.9) mL·kg<sup>-1</sup>·min<sup>-1</sup> (74% of matched controls, p=0.002). All other cardiorespiratory responses, except  $VE_{\text{peak}}$  in non-fatigued patients, were lower in patients than in controls; fatigued patients performed at a level ranging from 52% to 70% of controls, and non-fatigued patients at a level ranging from 70% to 84% (Table 4).

### DISCUSSION

To our knowledge, this is the first study to investigate cardiorespiratory responses to progressive CPET in patients who have suffered an a-SAH. Cardiorespiratory fitness was significantly lower in patients compared to sex- and age-matched controls. Although we hypothesized that the cardiorespiratory fitness would be particularly impaired in fatigued patients, this study shows that  $\dot{V}O_{2\text{peak}}$  was also limited in non-fatigued patients. Furthermore, this study demonstrates that progressive CPET can be safely performed in a substantial group of patients with a-SAH if medical pre-screening procedures are implemented.

The present study shows impaired cardiorespiratory fitness in patients with a-SAH; mean  $\dot{V}O_{2\text{peak}}$  was 69% of controls. Compared to patients with stroke, not caused by a-SAH, levels of cardiorespiratory fitness are somewhat higher.<sup>14</sup> This can be explained by the fact that the patients in our study had a relatively good functional outcome; there were no signs of paresis or spasticity. Therefore, they are more likely to maintain physical activities and preserve their cardiorespiratory fitness.<sup>29-31</sup> Further, premorbid physical inactivity, with reduced cardiorespiratory fitness, is a designated risk factor for stroke, whereas this is not known for patients with a-SAH.<sup>32, 33</sup>

Many factors could potentially contribute to a limited  $\dot{V}O_{2\text{peak}}$  in a-SAH. Increased oxygen uptake by the muscle cells in response to physical effort, requires increased pulmonary capacity and cardiac output. According to the present findings, patients showed both a lower  $VE_{\text{peak}}$  and a lower peak oxygen pulse. This may result from physical deconditioning, a mechanism that is supported by the fact that patients participated less in sports and/or moderate intensive physical activities.

**Table 4.** Cardiorespiratory fitness in fatigued and non-fatigued patients with a-SAH and control subjects.

Cardiorespiratory fitness mean (SD)	Fatigued (n=12)	Controls (n=12)	95% CI for the difference	p-value	Non-fatigued (n=16)	Controls (n=16)	95% CI for the difference	p-value
$\dot{V}O_{2peak}$ (mL·min <sup>-1</sup> )	1365 (322)	2199 (391)	-1148.4 to -518.9	<0.001 <sup>†</sup>	1840 (544)	2349 (667)	-827.4 to -191.9	0.004 <sup>†</sup>
$\dot{V}O_{2peak}$ (mL·kg <sup>-1</sup> ·min <sup>-1</sup> )	19.4 (4.1)	30.8 (5.0)	-13.4 to 4.9	<0.001 <sup>†</sup>	23.9 (6.9)	32.1 (6.9)	-12.2 to -4.1	0.001 <sup>†</sup>
$\dot{V}O_{2peak}$ (mL·kg FFM <sup>-1</sup> ·min <sup>-1</sup> )	31.1 (6.5)	46.3 (6.0)	-19.4 to -11.1	<0.001 <sup>†</sup>	36.4 (9.6)	45.7 (6.0)	-14.9 to -3.6	0.004 <sup>†</sup>
$\dot{V}E_{peak}$ (L·min <sup>-1</sup> )	54.3 (10.9)	83.8 (18.2)	-43.8 to -15.2	0.001 <sup>†</sup>	79.8 (26.7)	94.8 (28.9)	-30.5 to 0.39	0.055
$\dot{V}O_{2peak}/HR_{peak}$ (mL/beat)	9.8 (2.0)	13.5 (2.0)	-4.6 to -1.5	0.002 <sup>†</sup>	11.5 (2.6)	14.2 (4.0)	-4.4 to -0.80	0.008
$PO_{peak}$ (Watt)	104.0 (26.7)	200.2 (40.9)	-123.5 to -68.8	<0.001 <sup>†</sup>	150.8 (46.6)	215.1 (64.1)	-94.3 to -34.5	<0.001 <sup>†</sup>
$RR_{peak}$ (breaths·min <sup>-1</sup> )	34 (8)	35 (6)	-6.8 to 4.6	0.687	38 (8)	38 (9)	-6.5 to 6.9	0.954
$HR_{peak}$ (bpm)	146 (19)	163 (18)	-34.7 to -0.77	0.042	159 (24)	166 (11)	-20.0 to 4.7	0.208
$RER_{peak}$ ( $\dot{V}CO_2/\dot{V}O_2$ )	1.13 (0.09)	1.19 (0.07)	0.01 to -0.12	0.070	1.15 (0.08)	1.24 (0.07)	-0.15 to -0.03	0.005
$HR_{peak}$ % of predicted $HR_{max}$	85.8 (10.8)	95.0 (9.1)	-19.8 to 0.19	0.054	92.2 (13.0)	96.8 (5.6)	-11.7 to 2.4	0.183

Abbreviations: a-SAH, aneurysmal subarachnoid hemorrhage;  $\dot{V}O_{2peak}$ , peak oxygen consumption;  $\dot{V}E_{peak}$ , peak minute ventilation;  $HR_{peak}$ , peak heart rate;  $\dot{V}O_{2peak}/HR_{peak}$ , peak oxygen pulse;  $PO_{peak}$ , peak power output; RR, respiratory rate;  $HR_{peak}$ , peak heart rate;  $RER_{peak}$ , peak respiratory exchange ratio.

<sup>†</sup> Significantly different after Bonferroni correction adjusting for multiplicity:  $p=0.05/10=0.005$ .

Patients with a-SAH reached VAT at earlier stages of CPET than controls. This implies that anaerobic oxidation, with subsequent accumulation of lactate in the blood, starts during milder physical effort. Because the perceived physical exertion at VAT is found to be 'heavy',<sup>34</sup> reaching VAT at milder physical effort may impact the performance of daily activities. Although limitations in cardiorespiratory fitness impact daily physical functioning in stroke,<sup>15,35</sup> not caused by a-SAH, future research is needed to investigate its impact in patients with a-SAH.

Although non-fatigued patients had lower  $\dot{V}O_{2\text{peak}}$  than controls (74% of controls),  $\dot{V}O_{2\text{peak}}$  seems to be more impaired in fatigued patients (63% of controls). This can be explained by the fact that fatigued patients may be more prone to initiate a degenerative circle of physical deconditioning, in which fatigue leads to the avoidance of physical activities which consequently reduces the cardiorespiratory fitness, which may further increase fatigue complaints.<sup>36</sup> Associations are reported between cardiorespiratory fitness and fatigue among several non-stroke patient groups.<sup>9-12</sup> However, research on such relationships in stroke is limited.<sup>8</sup> Intervention studies are warranted to investigate whether improved levels of cardiorespiratory fitness reduces fatigue after a-SAH.

A recent report recommends exercise training as an integral component of stroke rehabilitation.<sup>15</sup> The present study indicates that patients with a-SAH may also benefit from exercise training. Previous studies showed that exercise training can improve  $\dot{V}O_{2\text{peak}}$  by 9-23% after stroke.<sup>37,38</sup> Moreover, Zedlitz et al. found additional benefits of graded exercise training on post-stroke fatigue.<sup>16</sup> Future intervention studies are warranted to investigate the beneficial effects of exercise training in patients with a-SAH.

The strength of the present study is the inclusion of a sex- and age-matched control group. Patients and controls performed identical CPET measurements which allowed better interpretation of the CPET results. The inclusion of a comparison group is a frequently used method studying cardiorespiratory responses in patients, including patients with stroke.<sup>39,40</sup>

### Study limitations

Some possible limitations should be discussed. First, selection bias may have occurred. Patients were excluded when they were not eligible to perform CPET. Therefore, we might have excluded those with a poor-grade a-SAH. Since these patients are more likely to have worse outcome, this might have led to an underestimation of the limitations in cardiorespiratory fitness. However, 18% of the sample had a poor-grade a-SAH (WFNS grade: IV-V), which is comparable to poor-grade a-SAH in the patient population where frequencies range from 18% to 24%.<sup>41</sup> It should be noted that more female patients

participated; only eight male patients participated (=29%). This can partly be explained by the fact that females have a higher risk of a-SAH than males;<sup>42</sup> the incidence of a-SAH in the Netherlands for men is 7.6 per 100,000 persons per year and for women 11.2 per 100,000 persons per year.<sup>43</sup> Because controls volunteered to participate, they might be more likely to take part in sports or moderate intensive daily physical activities. This might have led to an overestimation of the cardiorespiratory limitations after a-SAH. No appropriate norm data are available on participation in sports and/or moderate intensive daily physical activities. However, Dutch data on sports participation solely (75% of the Dutch population participates in sports activities),<sup>44</sup> suggest that our control group is representative for the Dutch population. Another limitation is that we do not know whether impaired cardiorespiratory fitness is a consequence of a-SAH or whether it was already present prior to the index event. However, premorbid physical inactivity and, inherently, impaired cardiorespiratory fitness is not a known risk factor for a-SAH. Considering the invasive CPET measurements, the present sample size is worth mentioning. However, the subdivision based on the presence of fatigue leads to smaller subgroups, which may be considered as a possible limitation. Because fatigue is one of the most distressing complaints, and cardiorespiratory fitness has not yet been studied in a-SAH, we considered it important to differentiate between fatigued and non-fatigued patients.

## **CONCLUSIONS**

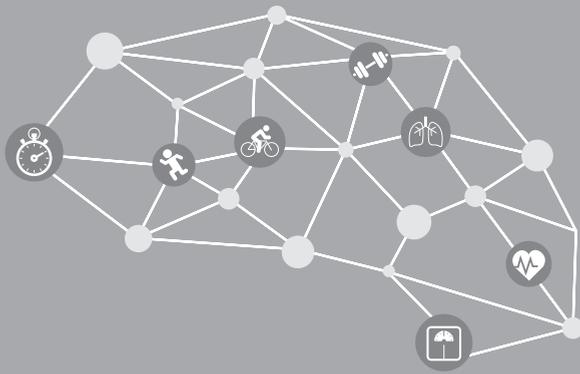
In conclusion, cardiorespiratory fitness is limited in patients with a-SAH, both in fatigued and non-fatigued patients. It seems that deficits in cardiorespiratory fitness were larger in fatigued patients than in non-fatigued patients, indicating the presence of a physical component in fatigue after a-SAH. Longitudinal studies are warranted to investigate the course of fatigue over time. Future research on interventions aiming at improving cardiorespiratory fitness seems necessary, and should evaluate whether higher levels of cardiorespiratory fitness reduces fatigue in a-SAH.

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# CHAPTER 5

**The six-minute walk test predicts  
cardiopulmonary fitness in patients  
with aneurysmal subarachnoid  
hemorrhage**

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## ABSTRACT

**Background:** Peak oxygen uptake ( $\dot{V}O_{2\text{peak}}$ ) established during progressive cardiopulmonary exercise testing (CPET) is the 'gold-standard' for cardiopulmonary fitness. However, CPET measurements may be limited in patients with aneurysmal subarachnoid hemorrhage (a-SAH) by disease related complaints, such as cardiovascular health-risks or anxiety. Furthermore, CPET with gas-exchange analyses require specialized knowledge and infrastructure with limited availability in most rehabilitation facilities.

**Objectives:** To determine whether an easy-to-administer six minute walk test (6MWT) is a valid clinical alternative to progressive CPET in order to predict  $\dot{V}O_{2\text{peak}}$  in patients with a-SAH.

**Methods:** Twenty-seven patients performed the 6MWT and CPET with gas-exchange analyses on a cycle ergometer. Univariate and multivariate regression models were made to investigate the predictability of  $\dot{V}O_{2\text{peak}}$  from the six minute walk distance (6MWD).

**Results:** Univariate regression showed that the 6MWD was strongly related to  $\dot{V}O_{2\text{peak}}$  ( $r=0.75$ ,  $p<0.001$ ), with an explained variance of 56% and a prediction error of  $4.12 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , representing 18% of mean  $\dot{V}O_{2\text{peak}}$ . Adding age and sex to an extended multivariate regression model improved the relationship ( $r=0.82$ ,  $p<.001$ ), with an explained variance of 67% and a prediction error of  $3.67 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  corresponding to 16% of mean  $\dot{V}O_{2\text{peak}}$ .

**Conclusions:** The 6MWT is an easy-to-administer submaximal exercise test that can be selected to estimate the cardiopulmonary fitness at an aggregated level, in groups of patients with a-SAH, which may help to evaluate interventions in a clinical or research setting. However, the relatively large prediction error does not allow for an accurate prediction in individual patients.

## INTRODUCTION

An aneurysmal subarachnoid hemorrhage (a-SAH) is a subtype of stroke caused by a ruptured intracranial aneurysm.<sup>1</sup> The incidence rate has remained stable over decades ranging from 6 to 8 per 100,000 persons per year.<sup>1, 2</sup> It is found that a-SAH has long-term consequences such as fatigue, depressive symptoms and problems in cognitive functioning, that may persist four years post-onset.<sup>3, 4</sup> Furthermore, half of the patients experience problems in resuming previous activities, 64% report on one or more participation restrictions, and only one-third is able to fully resume their previous occupation.<sup>4-7</sup>

Previously, we showed that the cardiopulmonary fitness was approximately 30% lower in patients with a-SAH compared to control subjects.<sup>8</sup> The beneficial effects of improved cardiopulmonary fitness in patients with stroke, not caused by a-SAH, are well-recognized and exercise training has become an integral component in stroke rehabilitation.<sup>9-11</sup> However, the benefits of improved cardiopulmonary fitness remain to be established in patients with a-SAH. The assessment of cardiopulmonary fitness may help to target and improve rehabilitation programs for patients with a-SAH.

The gold standard for measuring cardiopulmonary fitness is peak oxygen uptake ( $VO_{2peak}$ ) obtained with indirect calorimetry during progressive cardiopulmonary exercise testing (CPET).<sup>12</sup> However, disease-related complaints, such as cardiovascular health risks or anxiety, may limit the use of progressive CPET in patients with a-SAH.<sup>13, 14</sup> Moreover, progressive CPET measurement with gas exchange analyses requires specialized knowledge and infrastructure, with limited availability in most rehabilitation facilities.

The six minute walk test (6MWT) is an easy-to-administer submaximal exercise test, in which the covered distance walked within six minutes is measured.<sup>15</sup> The six minute walk distance (6MWD) is found to be predictive of  $VO_{2peak}$  in patients with cardiopulmonary disorders.<sup>16-18</sup> However, in patients with stroke, not caused by an a-SAH, the 6MWD seems to be less predictive of  $VO_{2peak}$ . Associations between 6MWD and  $VO_{2peak}$  range from 0.34 to 0.74.<sup>19</sup> The 6MWD seems to be more determined by the walking capacity rather than by  $VO_{2peak}$ .<sup>19-22</sup> Since patients with a-SAH usually do not suffer from neuro-motor lesions, such as paresis or spasticity, directly affecting the walking capacity,<sup>23, 24</sup> we hypothesize that the 6MWD is indicative of  $VO_{2peak}$  in patients with a-SAH. If we confirm our hypothesis, the 6MWT may be an easy-to-use instrument to assess the cardiopulmonary fitness, and would be of great value in daily clinical practice.

## METHODS

### Setting and participants

This cross-sectional study, entitled HIPS-Rehab, was part of the longitudinal observational study: 'Hypopituitarism In Patients after Subarachnoid haemorrhage study (HIPS)'.<sup>25</sup> This study describes measures of physical fitness that were obtained at six months post a-SAH. The study was approved by the Medical Ethics Committee of the Erasmus University Medical Center, and all participants gave written informed consent.

Patients with a-SAH admitted to the department of Neurology of the Erasmus Medical Center between June 2009 and June 2012 were eligible for inclusion when they were discharged from the Intensive Care Unit and aged  $\geq 18$  years. Diagnosis of a-SAH was confirmed by computerized tomography (CT) of the brain and, in cases with negative CT, by lumbar puncture. Presence and location of the aneurysm was determined by CT angiography and/or a digital subtraction angiography.

Excluded from the study were patients meeting any of the following criteria: hypothalamic or pituitary disease diagnosed prior to a-SAH; history of cranial irradiation; trauma capitis prior to a-SAH; other intracranial lesion apart from a-SAH; or other medical or psychiatric condition or laboratory abnormality that may interfere with the outcome of the study. Additional exclusion criteria regarding the CPET measurements were: aged  $\geq 70$  years, and absolute contra-indication for progressive CPET.

### Procedures

Contraindications and health risks for physical exercise were examined by treating physician using the guidelines for exercise testing and prescription, established by the American College of Sports Medicine (ACSM)<sup>26</sup> and the Physical Activity Readiness Questionnaire (PAR-Q).<sup>27</sup> Hereafter, 6MWT and progressive CPET were performed sequentially in this order. Sufficient resting periods were provided between tests. A sports physician served as an emergency back-up during progressive CPET.

#### *Six Minute Walk Test (6MWT)*

The 6MWT is an easy-to-administer submaximal exercise test and was applied as described by the American Thoracic Society.<sup>28</sup> The 6MWT showed good to excellent test-retest reliability after stroke.<sup>29</sup> Participants were instructed to walk as far as they could along a 30-m indoor, continuous track with a hard surface during a 6-min period. The 6MWT was not practiced beforehand, since this resembles clinical practice. Consistent encouragement was provided after each minute. Participants were allowed to take rest during the test, but were instructed to resume walking as soon as they were able to do

so.<sup>28</sup> The 6MWD (m) was registered at the end of the test. Heart rate (HR) was recorded using a HR monitor.

#### *Cardiopulmonary Exercise Test (CPET)*

Progressive CPET was performed on an electronically braked cycle ergometer, which is considered feasible and safe in patients with stroke who underwent pre-test medical screening.<sup>30</sup> A ramp protocol was implemented which was preceded by a 4-minute warm-up. Hereafter, the resistance increased every 10 seconds (for women: 12W/min, for men: 16W/min) to ensure that volitional exhaustion was reached within 8 to 14 minutes. The participants were instructed to pedal at a rate of 60 to 70 revolutions per minute. CPET was terminated when participants voluntarily stopped or unable to maintain the target pedal rate. CPET could also be terminated because of increased health risks, as prescribed in the guidelines of the ACSM.<sup>31</sup>

During progressive CPET, blood pressure was measured for safety reasons using an automatic system, and heart function was monitored continuously with a 12-lead electrocardiogram. Gas exchange analyses were applied by indirect calorimetry using a breath-by-breath oximetry analysing system. Before each measurement, volume and gas calibrations were performed. Peak oxygen uptake was defined as the highest mean oxygen uptake during 30 seconds of exercise and was expressed in absolute  $\dot{V}O_{2\text{peak}}$  ( $\text{mL}\cdot\text{min}^{-1}$ ) and  $\dot{V}O_{2\text{peak}}$  per kilogram body mass ( $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ).

Only data of participants that met at least one of the objective criteria for maximal physical exertion were included in the final analyses. The following criteria were used to objectively determine the intensity of maximal exercise testing: 1) respiratory exchange ratio (RER)  $>1.0$ ,<sup>32</sup> or 2) peak heart rate ( $\text{HR}_{\text{peak}}$ ) within 10 beats per minute (bpm) of the age-predicted maximum heart rate ( $\text{HR}_{\text{max}}$ ), calculated from the formula of Tanaka et al.:<sup>33</sup>

$$\text{HR}_{\text{max}} = 208 - (0.7 * \text{age})$$

As beta-blocker medication reduces  $\text{HR}_{\text{max}}$  by 25-30%,<sup>30</sup> the equation was adjusted for those with beta-blocker medication:

$$\text{HR}_{\text{max}} = 0.70 * [208 - (0.7 * \text{age})]$$

#### *Clinical characteristics*

The following clinical characteristics were collected to describe the study population: World Federation of Neurologic Surgeons (WFNS) grade,<sup>34</sup> Glasgow Coma Scale (GCS)

score,<sup>35</sup> location of aneurysm and treatment modality. Additionally, neurologic morbidity, such as paresis or spasticity, was examined and Body Mass Index (BMI) was calculated from height and body mass ( $\text{kg}/\text{m}^2$ ).

### **Statistical analyses**

Participants meeting the objective criteria for maximal exercise testing were included in the final analyses. All data are expressed as mean (SD) unless otherwise indicated. The assumptions for normality and linear regression analyses were met. To compare clinical characteristics of participants versus non-participants, independent t-tests were used for continuous data and chi-square tests were used for categorical data.

A univariate linear regression model was made, selecting  $\dot{V}O_{2\text{peak}}$  as dependent variable and 6MWD (m) as independent variable. In a multivariate linear regression model age and sex were added using step-wise regression with variables being added in a forward model. The explained variance ( $r^2$ ) and the correlation coefficient ( $r$ ) were analysed. Although there are no hard rules to describe correlational strength, we considered a correlation coefficient of  $r > 0.70$  as a strong correlation, representing a good estimation of the  $\dot{V}O_{2\text{peak}}$  at an aggregated group level.<sup>36</sup> Furthermore, the Standard Error of the Estimate (SEE), as a percentage of mean  $\dot{V}O_{2\text{peak}}$  was calculated to determine the magnitude of prediction error which reflects the prediction accuracy at an individual level.

Additionally, paired samples t-test was used to compare the 6MWD with normative values which were calculated from the formula established by Enright et al.<sup>37</sup> All analyses were performed using IBM SPSS Statistics, version 20, and a probability value of  $p < 0.05$  was considered statistically significant.

## **RESULTS**

Between June 2009 and June 2012, 241 patients were admitted to the ICU with a diagnosis of a-SAH, 84 were included in HIPS of which 52 volunteered to participate in HIPS-Rehab. Participants in HIPS-Rehab ( $n=52$ ) did not differ from non-participants ( $n=32$ ) regarding: sex ( $p=0.291$ ), age ( $p=0.996$ ), WFNS-grade ( $p=0.505$ ), GCS-score ( $p=0.136$ ), location of the aneurysm ( $p=0.469$ ), treatment modality ( $p=0.489$ ), and presence of hypopituitarism ( $p=0.353$ ) or hydrocephalus ( $p=0.559$ ).

Of the 52 patients included, 27 patients performed successful measurements of 6MWT and CPET (52%); nine were aged  $\geq 70$  years, seven could not perform CPET because of logistic reasons, five had absolute contraindications to CPET, two did not meet the ob-

jective criteria for maximal physical exertion, one was not able to perform CPET because of an additional injury and another one could not perform 6MWT because of visual impairment. Despite the fact that patients were younger (mean age difference=6.8 years; 95% CI of the difference: -12.94 to -0.057;  $p=0.033$ ), there were no significant differences compared with those who were excluded from the final analysis ( $n=25$ ). Table 1 presents characteristics of the participants.

Most patients had a ruptured aneurysm in the anterior circulation (63%), 78% underwent endovascular coiling, and 23 (85%) were graded to WFNS I or II and had a mean GCS-score of 13.7 (SD 2.3). Participants did not have neuro-motor deficits such as paresis or spasticity.

Although 21 participants (78%) had an increased health risk for physical exercise, there were no serious unexpected side-effects observed during or after 6MWT or progressive CPET. Outcome measures of 6MWT and CPET are presented in Table 2. Mean 6MWD was 498 (SD 98) m, which is significantly lower than the calculated mean norm values (557 (SD 70) m; 95% CI of the difference=-99.1 to -18.6;  $p=0.006$ ).<sup>37</sup> HR at the end of 6MWT

**Table 1.** Clinical characteristics.

Characteristics	Patients with a-SAH (n=27)
Sex, male n (%)	8 (30%)
Age (years), mean (SD)	53.0 (8.9)
Weight (kg), mean (SD)	74.8 (10.3)
BMI (kg/m <sup>2</sup> ), mean (SD)	25.9 (3.7)
WFNS grade, n (%)	
I	14 (52%)
II	9 (33%)
III	0
IV	3 (11%)
V	1 (4%)
Glasgow Coma Scale-score, mean (SD)	13.7 (2.3)
Location aneurysm, n (%)	
- Anterior circulation	17 (63%)
- Posterior circulation	10 (37%)
Treatment procedure, n (%)	
- Surgical clipping	6 (22%)
- Endovascular coiling*	21 (78%)

Abbreviations: BMI, Body Mass Index (kg/m<sup>2</sup>); WFNS grade, World Federation of Neurologic Surgeons grading system for subarachnoid hemorrhage.

**Table 2.** Results of the six-minute walk test and cardiopulmonary exercise test.

Exercise testing	Patients with a-SAH (n=27)
<b>6MWT, mean (SD)</b>	
6MWD (m)	498 (98)
HR (bpm)	114 (20)
<b>CPET, means (SD)</b>	
Time until $\dot{V}O_{2peak}$ (min:sec)	09:45 (01:50)
$\dot{V}O_{2peak}$ ( $\text{mL}\cdot\text{min}^{-1}$ )	1664.4 (500.8)
$\dot{V}O_{2peak}$ ( $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ )	22.3 (6.0)
$VE_{peak}$ ( $\text{L}\cdot\text{min}^{-1}$ )	70.4 (23.7)
Maximum Load (W)	132.9 (44.7)
$HR_{peak}$ (bpm)	152 (24)
$RER_{peak}$ ( $\dot{V}CO_2/\dot{V}O_2$ )	1.15 (0.08)

Abbreviations: 6MWT, 6-minute walk test; 6MWD, 6-minute walk distance; HR, heart rate; bpm, beats per minute;  $\dot{V}O_{2peak}$ , peak oxygen uptake;  $VE_{peak}$ , peak minute ventilation;  $HR_{peak}$ , peak heart rate; RER, respiratory exchange ratio.

was 114 (SD 20) bpm, reflecting 67% of predicted maximum HR (171 (SD 6) bpm). Results for CPET measurement showed a mean  $\dot{V}O_{2peak}$  of 22.3 (SD 6.0)  $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , with a mean peak HR of 152 (SD 24) bpm, reflecting 89% of predicted maximum HR (171 (SD 6) bpm).

Univariate linear regression model, with  $\dot{V}O_{2peak}$  as dependent variable and 6MWD as independent variable revealed a strong relationship ( $r=0.75$ ;  $\beta=0.05$ ; 95% CI of  $\beta$ : 0.03 to 0.06;  $p<0.001$ ), with an explained variance of 56% (Table 3). SEE was 4.12  $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , representing 18% of mean  $\dot{V}O_{2peak}$ . Figure 1 shows the relationship between  $\dot{V}O_{2peak}$  and

**Table 3.** Univariate and multivariate linear regression analysis with  $\dot{V}O_{2peak}$  ( $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) as dependent variable and the 6-minute walk distance (6MWD) as independent variable.

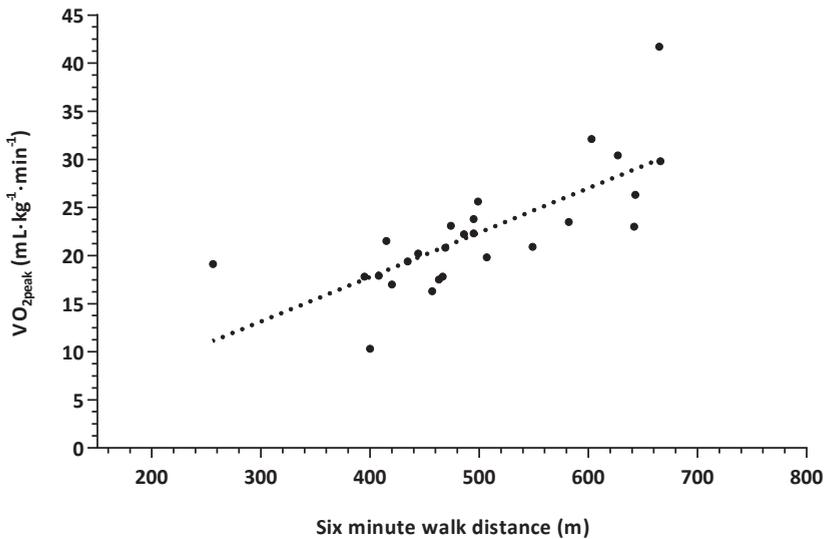
	$\beta$ (95% CI) †	$p$	$R$	$r^2$	SEE	(SEE/mean)*100†
<b>Univariate</b>						
constant	-0.70		0.75	0.56	4.12	18%
6MWD (m)	0.05 (0.03 to 0.06)	<0.001				
<b>Multivariate#</b>						
constant	12.10		0.82	0.63	3.67	16%
6MWD	0.04 (0.03 to 0.06)	<0.001				
Age	-0.21 (-0.38 to -0.04)	0.017				
Sex	1.52 (-1.76 to 4.80)	0.349				

Abbreviations: SEE, Standard Error of the Estimate.

‡ Unstandardized  $\beta$ -coefficients;

† SEE expressed as percentage of mean  $\dot{V}O_{2peak}$ ;

# In the multivariate model sex and age were included; sex was coded 0 for men and 1 for women.



**Figure 1.** Relationship between peak oxygen uptake ( $\dot{V}O_{2peak}$ ) and 6-minute walk distance.

6MWD. The extended multivariate linear regression model was significant ( $p < 0.001$ ), with an explained variance of 67% and SEE of  $3.67 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , representing 16% of mean  $\dot{V}O_{2peak}$  (Table 3). In addition to the 6MWD ( $\beta = 0.04$ ; 95% CI of  $\beta$ : 0.03 to 0.06;  $p < 0.001$ ), we found that age significantly contributes to the prediction of  $\dot{V}O_{2peak}$  ( $\beta = -0.21$ ; 95% CI of  $\beta$ : -0.38 to -0.04;  $p = 0.017$ ), whereas sex did not ( $\beta = 1.52$ ; 95% CI for  $\beta$ : -1.76 to 4.80;  $p = 0.349$ ).

## DISCUSSION

The present study examined whether the 6MWT is a valid alternative to progressive CPET to predict the cardiopulmonary fitness after a-SAH. A significant and strong correlation was found between the 6MWD and  $\dot{V}O_{2peak}$  ( $r = 0.82$ ), with a prediction error representing 16% of mean  $\dot{V}O_{2peak}$ . Since post-stroke exercise programs improve cardiopulmonary fitness by 9-23%,<sup>38</sup> we consider the prediction error of 16% too large to accurately predict  $\dot{V}O_{2peak}$  at an individual level. However, the 6MWT can be used to predict cardiopulmonary fitness at an aggregated level in groups of patients with a-SAH in clinical and research settings.

According to Outermans et al., correlational strength between  $\dot{V}O_{2peak}$  and 6MWD in patients with stroke, not caused by a-SAH, ranges from 0.34-0.74.<sup>19</sup> It is reported that this relationship in stroke is more determined by balance problems and neuro-motor

impairments, affecting walking ability, rather than by a limited  $\dot{V}O_{2peak}$ .<sup>19,20</sup> Patterson et al. showed that the variance in 6MWD in patients with stroke was explained by  $\dot{V}O_{2peak}$  for those who walked more quickly, and by balance for those who walked more slowly.<sup>39</sup> In our study, the relatively strong relationship between 6MWD and  $\dot{V}O_{2peak}$  can be explained by the fact that patients with a-SAH have relatively mild neurologic morbidity that interferes with the walking ability of patients.

The present findings are in line with studies in patients with cardiopulmonary disorders, where correlational strength between the 6MWD and  $\dot{V}O_{2peak}$  ranges from 0.68 to 0.82.<sup>40,41</sup> Ross et al.<sup>17</sup> studied the predictability of  $\dot{V}O_{2peak}$  from the 6MWD by analysing the magnitude of the SEE across 10 different studies, including 1,083 cardiopulmonary patients. They found moderate-to-strong relationships and reported on a poor prediction accuracy as well; they concluded that the 6MWT can be used to estimate mean  $\dot{V}O_{2peak}$  at an aggregated level, but that the 6MWT cannot predict  $\dot{V}O_{2peak}$  at an individual level.

In patients with a-SAH, mean 6MWD was found to be 498m, which is higher compared to patients with other types of stroke (6MWD ranges from 216-401 m).<sup>19</sup> However, the mean 6MWD is 25% lower compared to that of sex and age-matched norm values, suggesting compromised cardiopulmonary fitness.<sup>37</sup>

Five participants had absolute contraindications for progressive CPET and the majority had increased health risks for physical exercise. This emphasizes the need for safe and valid submaximal alternatives to progressive CPET in a-SAH. Since the 6MWT cannot accurately predict  $\dot{V}O_{2peak}$  at an individual level, studies are warranted to investigate other options. Future research may consider the use of submaximal cycle ergometer protocols. A recently introduced submaximal cycle ergometer test by Ekblom-Bak et al. predicts  $\dot{V}O_{2peak}$  with a small prediction error that represents 9.3% of mean  $\dot{V}O_{2peak}$ .<sup>42</sup> However, its validity needs to be determined in various patient categories.

### **Study limitations**

Since prediction models often require large study samples, our sample size can be considered a limitation. However, considering the invasive CPET measurement and the rather low prevalence rate of a-SAH, the present sample size is worth mentioning in the stroke literature. Another limitation is that selection bias may have occurred towards patients who are willing to perform exercise until voluntary exhaustion, which may have affected the external validity of our findings. However, apart from age, participants did not significantly differ from non-participants (also not for WFNS grade and GCS-score at admission). Finally, for pragmatic reasons, the 6MWT and the CPET were performed

on a single day. Although we provided ample resting time, ideally the tests should be performed on separate days to provide sufficient rest between the tests.

## CONCLUSIONS

The 6MWD was strongly related to  $\dot{V}O_{2\text{peak}}$  in patients with a-SAH. Therefore, the 6MWT can be used to predict mean  $\dot{V}O_{2\text{peak}}$  at an aggregated group level. This is relevant for the evaluation of therapy programs in the clinical setting and for research purposes. However, the prediction error was too large to accurately predict  $\dot{V}O_{2\text{peak}}$  in individual patients. Since the importance of cardiopulmonary fitness is well-recognized across different patient groups, easy-to-administer submaximal exercise tests need to be identified, to target and improve rehabilitation for patients with a-SAH.

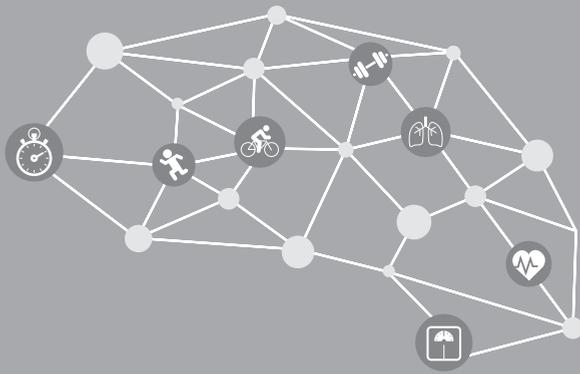
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# CHAPTER 6

**Physical fitness remains low over the first year after aneurysmal subarachnoid hemorrhage, relates to physical inactivity and functional outcome, and is predicted by surgical clipping**

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[Submitted]

## ABSTRACT

**Background:** Physical inactive and sedentary lifestyles and low functional outcome are thought to impact the level of physical fitness in patients with a-SAH. However, longitudinal changes in physical fitness and relationships with activities and functional outcome have not been studied in a-SAH.

**Objective:** To evaluate the level of physical fitness in the first year after a-SAH, and to explore longitudinal relationships with physical activity (PA), sedentary behavior (SB) and functional outcome. Additionally, we have evaluated whether physical fitness could be predicted by disease-related characteristics.

**Design:** Prospective one-year follow-up.

**Methods:** Fifty-two patients performed exercise testing at six and twelve months post a-SAH. Cardiopulmonary exercise testing and isokinetic dynamometry were applied to determine the peak oxygen uptake ( $\dot{V}O_{2peak}$ ) and the peak torque of the knee extensors ( $PT_{ext}$ ) and flexors ( $PT_{flex}$ ). In addition, PA and SB were evaluated by accelerometer-based activity-monitoring. The functional outcome was assessed by the FIM+FAM. Disease-related characteristics were collected at hospital intake.

**Results:** All fitness parameters were lower compared to reference values at both six and twelve months post a-SAH (ranging from 18-28%). Positive relationships were found between PA on the one hand and  $\dot{V}O_{2peak}$  and  $PT_{flex}$  on the other, and between FIM+FAM-scores and  $PT_{ext}$  and  $PT_{flex}$ . Further, patients who underwent surgical clipping had lower  $\dot{V}O_{2peak}$  and  $PT_{flex}$ .

**Limitations:** Longitudinal observations cannot confirm causality.

**Conclusions:** Levels of physical fitness remain low over the first year after a-SAH. Patients who were physically more active had higher physical fitness, whereas patients with impaired functional outcome, or treated with surgical clipping are at risk of low physical fitness. Exercise interventions are warranted and should focus on the promotion of PA and target patients with impaired functional outcome or those who had been treated with surgical clipping.

## INTRODUCTION

Aneurysmal subarachnoid hemorrhage (a-SAH) is a life-threatening condition and accounts for 3% to 5% of all stroke cases.<sup>1</sup> Depending on its severity, a-SAH is associated with a mortality rate that ranges from 40% to 60% within the first month.<sup>2</sup> The incidence rate ranges from 4 to 10 per 100,000 persons per year.<sup>2</sup> Most patients regain independence in daily functioning.<sup>3</sup> However, more than two-thirds experience restrictions in daily activities and cannot regain pre-morbid level of participation.<sup>4,5</sup> Since the mean age at which a-SAH occurs is reasonably young at 55 years,<sup>2</sup> these restrictions can have a devastating and long-lasting impact on daily life.

Because most patients with a-SAH experience restrictions in daily activities, patients may be predisposed to inactive and sedentary lifestyles. As a consequence, patients may be at risk of low physical fitness.<sup>6</sup> Physical fitness refers to a set of physiological attributes that a person has or achieves, and confers the ability to carry out daily activities without undue fatigue.<sup>6</sup> Cardiorespiratory fitness and knee muscle strength are important aspects of physical fitness and found to be indicative of independent daily living.<sup>7,8</sup> Previous cross-sectional studies showed impaired cardiorespiratory fitness (62% to 77% of controls) and knee muscle strength (64% to 78% of controls) at six months post a-SAH.<sup>9</sup> However, longitudinal studies are warranted to evaluate changes in physical fitness and related factors over time, which would provide important clinical information to target therapeutic interventions.

Studies in patients with stroke, other than a-SAH, showed that the cardiorespiratory fitness and knee muscle strength were consistently low over time, ranging from 48% to 87%, and from 25% to 83% of controls, respectively.<sup>10,11</sup> Deficits were found up to 5 years post onset, and exercise training has become an integral component in stroke rehabilitation.<sup>12</sup> Patients with stroke who were less physically active, more severely disabled, or functionally more compromised are at risk of low physical fitness.<sup>13-15</sup> Since the origin of brain damage differs between patients with ischemic or hemorrhagic stroke and patients with a-SAH (focal vs. diffuse brain damage), it is not clear whether these factors play a similar role in fitness after a-SAH. In a-SAH, the severity of initial outcome, treatment procedure (surgical clipping vs. endovascular coiling), location of aneurysm (anterior vs. posterior), and pituitary dysfunction are known predictors of long-term outcome.<sup>2,3,16</sup> Therefore, these factors may play a role in physical fitness after a-SAH as well.

The primary goal was to evaluate the level of physical fitness over the first year after a-SAH, and to explore longitudinal relationships with physical activity, sedentary behavior and functional outcome. Secondary, we have evaluated whether physical fitness can be

predicted by disease-related characteristics to identify patients at risk of low physical fitness. Repeated measurements of physical fitness, physical activity, sedentary behavior and functional outcome were performed at six and twelve months post a-SAH. We hypothesized that physical fitness remains low over the first year, and that low levels of physical fitness are related to physical inactive and sedentary lifestyles. Further, we hypothesized that patients with more severe a-SAH at hospital intake and those who had been treated with surgical clipping have lower physical fitness.

## **METHODS**

### **Participants and design**

This study entitled HIPS-Rehab and was part of the 'Hypopituitarism In Patients after Subarachnoid hemorrhage (HIPS) study'.<sup>17</sup> Data collection, clinical definitions of a-SAH and inclusion criteria have been published previously.<sup>9, 17</sup> Personal and disease-related characteristics were collected at hospital intake, and measures of physical fitness, physical behavior and functional outcome were assessed at six and twelve months post onset. This study was approved by the Medical Ethics Committee of the Erasmus MC. All participants provided written informed consent.

### **Primary outcome**

Physical fitness was assessed by analyzing the cardiorespiratory fitness and isokinetic knee muscle strength. Safety procedures were implemented prior to exercise testing. All participants were screened for medical contraindications to exercise by treating neurologist. In addition, all participants fulfilled the Physical Activity Readiness Questionnaire.<sup>18</sup> Exercise testing was not carried out if there was any suspicion of an underlying cardiovascular or pulmonary pathology that may increase the risk of medical complications during exercise testing.

Cardiorespiratory fitness was assessed by cardiopulmonary exercise testing (CPET) on a cycle ergometer (Jaeger ER800, Jaeger Toennies, Breda, The Netherlands). CPET was preceded by a 4-minute warm-up without resistance after which the resistance increased automatically every 10 seconds to ensure that voluntary exhaustion was reached within 8-14 minutes (increment for women: 12W/min; men: 16W/min). The test stopped when the participants were not able to maintain the target pedal rate (60-70 revolutions per minute). CPET could also be terminated because of medical complications, as prescribed by the guidelines of the American College of Sports Medicine (ACSM).<sup>19</sup> During CPET, gas exchanges were analyzed by indirect calorimetry (Oxycon Pro, ViaSys Healthcare, Houten, The Netherlands). Peak oxygen uptake ( $VO_{2peak}$ ) was measured at peak physical

work rate which was defined as the highest mean peak value during 30 sec of exercise, and was expressed in relative  $\dot{V}O_{2\text{peak}}$  per kilogram body mass ( $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ).

In order to determine whether participants reached maximal physical exertion we used the following objective criteria: (I)  $\text{RER} > 1.0$ <sup>20</sup> or (II)  $\text{HR}_{\text{peak}}$  within 10 bpm of the age predicted maximum heart rate ( $\text{HR}_{\text{max}}$ ), calculated from the following formula of Tanaka et al.<sup>21</sup>:

$$\text{HR}_{\text{max}} = 208 - (0.7 * \text{age})$$

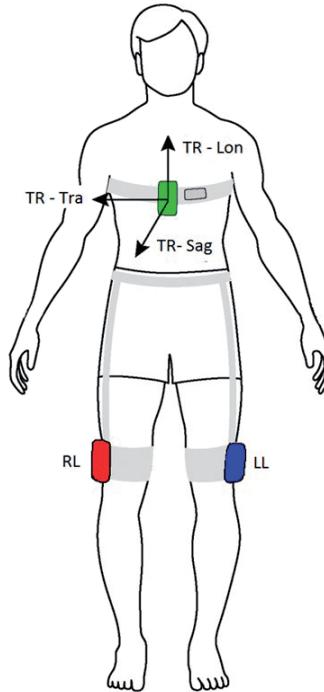
As beta-blocker medication reduces  $\text{HR}_{\text{max}}$  by approximately 25-30%,<sup>22</sup> we adjusted the formula for participants with beta-blocker medication:

$$\text{HR}_{\text{max}} = 0.70 * [208 - (0.7 * \text{age})]$$

Knee muscle strength was assessed by isokinetic dynamometry using the Biodex Dynamometer (Biodex, Shirley, New York, USA). Adjustable seatbelts were used to minimize body movements. The lateral femoral epicondyle was aligned with the rotational axis of the dynamometer. Peak torque (PT) of the knee extensors ( $\text{PT}_{\text{ext}}$ ) and flexors ( $\text{PT}_{\text{flex}}$ ) were recorded in torque (Nm) and corrected for body mass ( $\text{Nm}\cdot\text{kg}^{-1}$ ). The test protocol involved 5 maximal knee extension and flexion contractions at  $60^\circ/\text{s}$ . PT was considered as the maximum torque generated throughout one series of repetitions. We calculated the average PT of both limbs because there were no significant differences in PT between the left and right lower limb.

### Secondary outcome

Objective measures of PA and SB were evaluated by accelerometer-based activity monitoring (VitaMove, 2M Engineering, Veldhoven, The Netherlands).<sup>23</sup> The VitaMove consists of three individual body fixed recorders (attached to sternum and both legs) (Figure 1). The recorders are wirelessly connected and synchronized every 10 sec. Each recorder has its own battery supply and accelerometer (Freescale MMA7260Q, Denver, USA). The VitaMove demonstrates validity for quantifying body postures and movements in healthy subjects, and in different patient populations.<sup>23, 24</sup> Participants wore the VitaMove on weekdays, except during swimming, bathing and sleeping. The intended duration of measurement was three consecutive days, with a minimum of one day.<sup>25</sup> Participants were instructed to continue their ordinary daily activities. The principles of measurement were explained after all measurements were completed to avoid measurement bias. Participants kept activity diaries to report reasons of non-wear periods. Accelerometer data were uploaded to a computer for kinematic analyses using VitaScore (VitaScore BV, Gemert, The Netherlands).<sup>23</sup> The following outcome measures



**Figure 1.** Placement of the VitaMove activity monitor.

Abbreviations: TR, trunk sensor; RL, right leg sensor; LL, left leg sensor; Lon=longitudinal axis; Sag=sagittal axis; Tra=transversal axis

were calculated as the mean of available measurement days: duration of PA (including walking, cycling, running, and non-cyclic movements; expressed as a percentage of a 24-hr period) and duration of SB (including lying and sitting activities; expressed as a percentage of waking hours).

Functional outcome was assessed by treating neurologist using the Functional Independence Measure and Functional Assessment Measure (FIM+FAM).<sup>26</sup> The FIM+FAM consists of 30 items and evaluates functional independence by examining self-care, transfers and mobility, communication, and cognitive and psychosocial daily functioning (FIM+FAM-scores ranging from 1 'total dependence' to 7 'complete independence'). The FIM+FAM showed excellent validity and reliability in patients with stroke.<sup>26</sup>

Age (in years) and sex were recorded. The following disease-related characteristics were collected at hospital intake: (I) severity of a-SAH according to the Glasgow Coma Scale (GCS)-score; (II) location of the aneurysm (anterior vs. posterior); (III) treatment procedure (surgical clipping vs. endovascular coiling); (iv) a-SAH complications (re-bleed, delayed cerebral ischemia, hyponatremia, and hydrocephalus); and (v) pituitary dysfunction.

## Statistical analyses

All data are expressed as mean (SD) unless otherwise indicated. Differences in clinical characteristics (including sex, age severity of a-SAH (GCS-score), treatment procedure, and location of the aneurysm) between participants in HIPS-Rehab (n=52) and those who did not participate (but included in HIPS; n=32) were verified by independent t-tests for interval variables and by  $\chi^2$ -tests for categorical variables. Descriptive statistics were used to describe personal and disease-related characteristics. Parametric tests were used because the Shapiro- Wilk test showed that physical fitness data were normally distributed:  $\dot{V}O_{2peak}$  (W=0.979, p=0.325),  $PT_{ext}$  (W=0.984, p=0.453) and  $PT_{flex}$  (W=0.972, p=0.082).

Linear mixed models were created to analyze changes in the estimated mean  $\dot{V}O_{2peak}$ ,  $PT_{ext}$  and  $PT_{flex}$  over follow-up time. Time (follow-up visit) was entered in the model as a predictor of the dependent outcome. Linear mixed models were also created to explore time-dependent relationships between physical fitness (separate models for  $\dot{V}O_{2peak}$ ,  $PT_{ext}$  and  $PT_{flex}$ ) and one of the following factors: PA (%24h), SB (%waking hours) and FIM+FAM (range 1-7). The following fixed factors were entered to study whether disease-related characteristics can predict physical fitness: GCS-score (range 1-15), location of the aneurysm (0=anterior, 1=posterior), treatment procedure (0=clipping, 1=coiling) and pituitary dysfunction (0=no, 1=yes).

Prediction equations were used to predict the level of physical fitness of patients with a-SAH.<sup>27,28</sup> For  $VO_{2peak}$  we used the formula established by Fairbairn et al. (1994),<sup>27</sup> for men:  $VO_{2peak} = 23 * height + 11.7 * weight - 31 * age - 332$ ; and for women:  $VO_{2peak} = 15.8 * height + 8.99 * weight - 27 * age + 207$ . Further,  $\dot{V}O_{2peak}$  was classified according to the classification of the Cooper Institute;<sup>28</sup>  $\dot{V}O_{2peak}$  levels below the 20<sup>th</sup> percentile are considered 'very low', and have been associated with an increased all-cause mortality.<sup>29</sup> For maximal isokinetic  $PT_{ext}$  and  $PT_{flex}$  we used the norm values gathered by Sunnerhagen et al. (2000).<sup>31</sup>

Linear mixed models are flexible in handling missing values and these models take into account the covariance between measurements within patients. Each model was adjusted for sex (0=women, 1=men) and age. Statistically, sex and age were not always significant confounders, but were kept in each model because these factors are considered of fundamental importance in research on physical fitness,<sup>32</sup> leading to the following linear mixed model equation:

$$Y(\text{Fitness}) = \beta_0 + \beta_1 \cdot \text{Visit} + \beta_2 \cdot \text{Age} + \beta_3 \cdot \text{Sex} + \beta_4 \cdot \text{Factor} + \varepsilon$$

We reported estimated  $\beta$ -coefficients, 95% confidence intervals and p-values. The significance level was set at  $p < 0.05$ . Bonferroni correction was applied to adjust for type I error for multiple testing (SPSS Inc, Chicago, IL).

## RESULTS

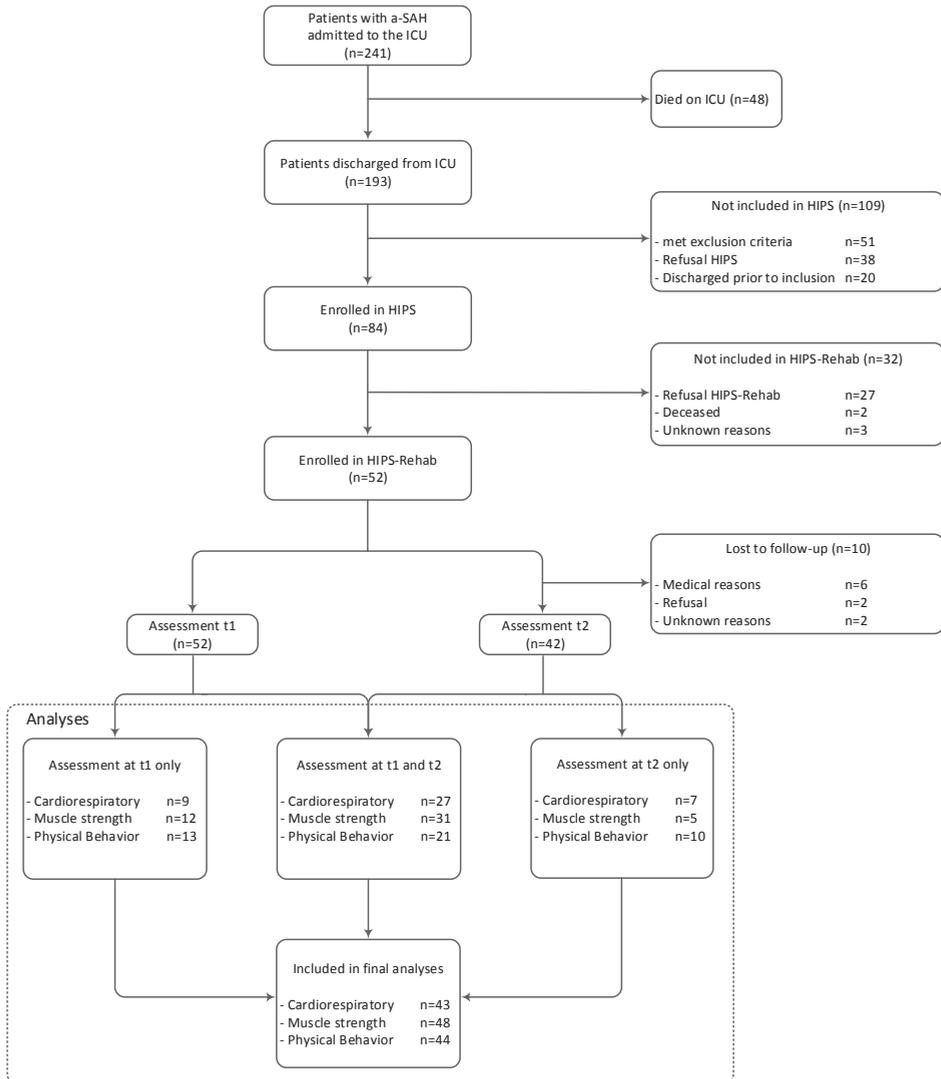
In total, 241 patients were admitted to the Intensive Care Unit with a diagnosis of a-SAH<sup>17</sup>; of the 84 eligible patients 52 participated in the present study. Patient characteristics are presented in Table 1. Participants in HIPS-Rehab (n=52) did not differ from those who did not participate (but included in HIPS; n=32) with respect to: sex ( $p=0.291$ ), age ( $p=0.996$ ), severity of a-SAH as determined by GCS-score ( $p=0.136$ ), treatment procedure ( $p=0.489$ ) and location of the aneurysm ( $p=0.469$ ). Fifty-two participants were assessed at six months, and 42 were assessed at twelve months post onset. However, data of most patients could be included in the final analyses because linear mixed models allow patients in the analyses for who some of the data is missing (Figure 2 presents a detailed flow diagram).

Data were not available for all participants at both follow-up times. CPET data of 43 patients were included in the final analyses (83% of the sample). In total, six patients were not able to perform CPET due to contraindications (n=3), logistical reasons (n=2) and because of an additional injury (n=1).

**Table 1.** Patient characteristics.

Characteristics	Patients with a-SAH (n=52)
Age (years), mean (SD)	56.1 (13.5)
Sex (men), n(%)	16 (31)
GCS-score, mean (SD)	13.5 (2.1)
Location aneurysm, n(%)	
- Anterior	31 (60)
- Posterior	21 (40)
Treatment procedure, n(%)	
- Endovascular coiling	47 (79)
- Surgical clipping	11 (21)
Complications, n (%)	
- Re-bleed,	0 (-)
- Delayed cerebral ischemia	7 (13%)
- Hyponatremia	6 (12%)
- Hydrocephalus	13 (25%)
Pituitary dysfunction, yes, n (%)	24 (46%)

Note: Data are presented as mean (SD) or n (%).

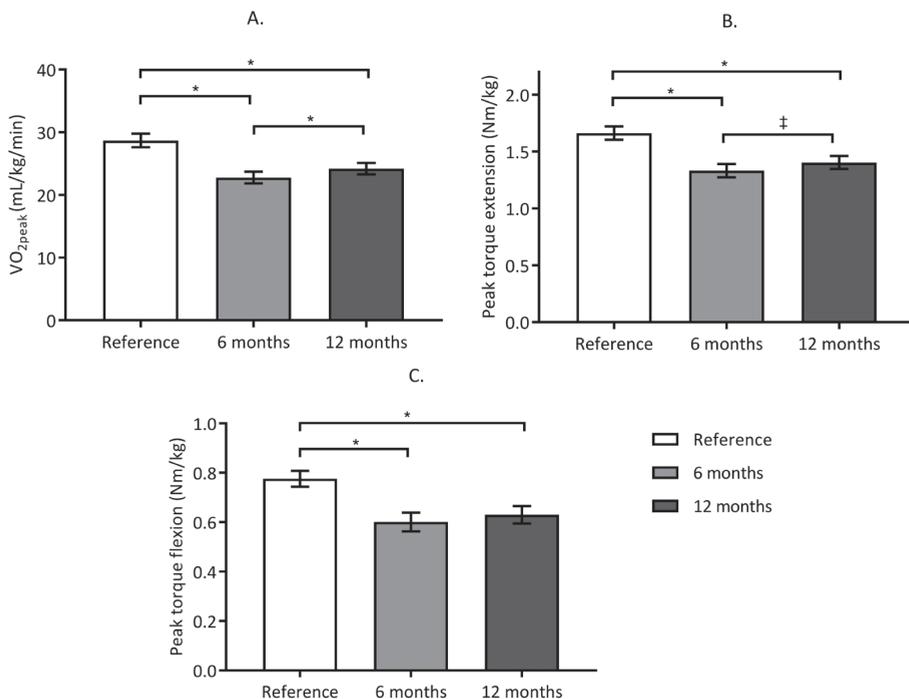


**Figure 2.** Flow diagram.

Furthermore, CPET data of three patients did not meet the objective criteria for maximal physical exertion and were excluded. In total nine patients with successful CPET had beta-blocker medication. Isokinetic dynamometry data of 48 patients were included (92% of the sample); three were not able to perform isokinetic dynamometry because of medical reasons and one because of logistical reasons. Activity monitoring data of 44 patients were included (85% of the sample); measurements in four patients were lost due to technical failure, three did not perform measurement because of logistical reasons and one patients refused.

## Physical fitness

Figure 3 shows a graphic presentation of the differences in the estimated  $\dot{V}O_{2\text{peak}}$ ,  $PT_{\text{ext}}$  and  $PT_{\text{flex}}$  between patients and reference at six and twelve months, respectively. The estimated mean  $\dot{V}O_{2\text{peak}}$  at six and twelve months were significantly lower than reference values: 26% lower at six and 21% lower at twelve months ( $p < 0.001$ ).<sup>27</sup> At six and twelve months, the  $\dot{V}O_{2\text{peak}}$  was considered 'fair' in respectively 29% and 30% of the patients, and 'very low' in respectively 43% and 39%.<sup>28</sup> Analyzing individual change (criterion:  $\pm 2.0 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ), showed that the  $\dot{V}O_{2\text{peak}}$  improved in 30%, remained stable in 48% and deteriorated in 22% of the patients.<sup>30</sup> The knee muscle strength was also lower compared to reference values at both six ( $PT_{\text{ext}}$  was 22% lower and  $PT_{\text{flex}}$  28%;  $p < 0.001$ ); and twelve months ( $PT_{\text{ext}}$  was 18% lower and  $PT_{\text{flex}}$  22%;  $p < 0.001$ ).<sup>31</sup>



**Figure 3.** Graphic presentation of the estimated mean(SE) for  $\dot{V}O_{2\text{peak}}$  (A.), peak torque knee extension (B.), and peak torque knee flexion (C.) at six and twelve months post a-SAH compared to reference values.

All CPET measurements were terminated because of volitional fatigue. The estimated mean  $\dot{V}O_{2\text{peak}}$  increased +6.2% (estimated mean difference =  $1.417 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ;  $p = 0.027$ ), while there was a nonsignificant trend for an increase of 5.1% in  $PT_{\text{ext}}$  (estimated mean difference =  $0.071 \text{ Nm}\cdot\text{kg}^{-1}$   $p = 0.061$ ) (Table 2). The estimated mean  $PT_{\text{flex}}$  did not change over time (estimated mean difference =  $0.026 \text{ Nm}\cdot\text{kg}^{-1}$   $p = 0.281$ ). Although patients man-

aged to exercise towards acceptable cardiorespiratory limits at both follow-up times, the estimated mean  $\text{RER}_{\text{peak}}$  at six months was lower compared to twelve months, 1.13 (SE 0.01) vs. 1.19 (SE 0.02), respectively ( $p < 0.001$ ). Further, the estimated  $\beta$ -coefficients showed that women had 28% lower  $\dot{\text{V}}\text{O}_{2\text{peak}}$  than men and  $\dot{\text{V}}\text{O}_{2\text{peak}}$  decreased 8% per 10 years of age.

**Table 2.** Estimated mean (SE) values of  $\dot{\text{V}}\text{O}_{2\text{peak}}$ , knee extensor and flexor strength, and daily physical activity and sedentary behavior with significance level of change over time.

	6 months (t1)	12 months (t2)	$\Delta$ t1-t2 <sup>#</sup>	95% CI for $\Delta$	p-value
$\dot{\text{V}}\text{O}_{2\text{peak}}$ (mL·kg <sup>-1</sup> ·min <sup>-1</sup> )	22.79 (0.94)	24.20 (0.91)	+1.417	0.170 to 2.664	0.027 <sup>*</sup>
$\text{HR}_{\text{peak}}$ % of predicted $\text{HR}_{\text{max}}$	88.59 (2.37)	90.42 (2.32)	+1.824	-1.398 to 5.054	0.255
$\text{RER}_{\text{peak}}$ ( $\text{VCO}_2/\text{VO}_2$ )	1.13 (0.01)	1.19 (0.02)	+0.058	0.034 to 0.081	<0.001*
$\text{PT}_{\text{ext}}$ (Nm·kg <sup>-1</sup> )	1.38 (0.06)	1.45 (0.06)	+0.071	-0.004 to 0.146	0.061 <sup>‡</sup>
$\text{PT}_{\text{flex}}$ (Nm·kg <sup>-1</sup> )	0.61 (0.04)	0.64 (0.04)	+0.026	-0.022 to 0.073	0.281

Abbreviations: CI, confidence interval;  $\dot{\text{V}}\text{O}_{2\text{peak}}$ , peak oxygen uptake;  $\text{HR}_{\text{peak}}$ , peak heart rate;  $\text{RER}_{\text{peak}}$ , peak respiratory exchange ratio;  $\text{PT}_{\text{ext}}$ , Peak Torque extension;  $\text{PT}_{\text{flex}}$ , Peak Torque flexion.

Note: All factors were entered separately in the model with adjustment for sex and age.

<sup>#</sup>Estimated mean difference (t1 -t2);

<sup>\*</sup>Significant difference ( $p < 0.05$ );

<sup>‡</sup>Nonsignificant trend for a difference ( $p < 0.10$ ).

## Determinants of physical fitness

Table 3 presents the results of the linear mixed models, evaluating the determinants of physical fitness. Total PA (%24h) was positively associated with  $\dot{\text{V}}\text{O}_{2\text{peak}}$  (estimated  $\beta = 0.638$  mL·kg<sup>-1</sup>·min<sup>-1</sup>;  $p = 0.006$ ) and  $\text{PT}_{\text{flex}}$  (estimated  $\beta = 0.018$  Nm·kg<sup>-1</sup>;  $p = 0.037$ ), indicating that patients who were physically more active had higher cardiorespiratory fitness and knee flexion strength. The FIM+FAM score was significantly related to  $\text{PT}_{\text{ext}}$  (estimated  $\beta = 0.125$  Nm·kg<sup>-1</sup>;  $p = 0.004$ ) and  $\text{PT}_{\text{flex}}$  (estimated  $\beta = 0.057$  Nm·kg<sup>-1</sup>;  $p = 0.042$ ), indicating that patients with lower functional outcome had lower knee flexion and extension strength. There was no evidence for a relationship between SB and physical fitness.

Further, patients who had been treated with surgical clipping had 22% lower  $\dot{\text{V}}\text{O}_{2\text{peak}}$  (estimated  $\beta = -4.946$  mL·kg<sup>-1</sup>·min<sup>-1</sup>;  $p = 0.008$ ) and 29% lower  $\text{PT}_{\text{ext}}$  (estimated  $\beta = -0.176$  Nm·kg<sup>-1</sup>;  $p = 0.029$ ) compared to those who underwent endovascular coiling. Figure 4 presents the change in physical fitness over the first year, specified by treatment procedure (surgical clipping vs. endovascular coiling). Other baseline characteristics of interest such as GCS-score, location of the aneurysm and pituitary dysfunction were not associated with physical fitness.

**Table 3.** Determinants of cardiorespiratory fitness ( $\dot{V}O_{2peak}$  in  $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) and knee muscle strength ( $PT_{ext}$  and  $PT_{flex}$  in  $\text{Nm}\cdot\text{kg}^{-1}$ ).

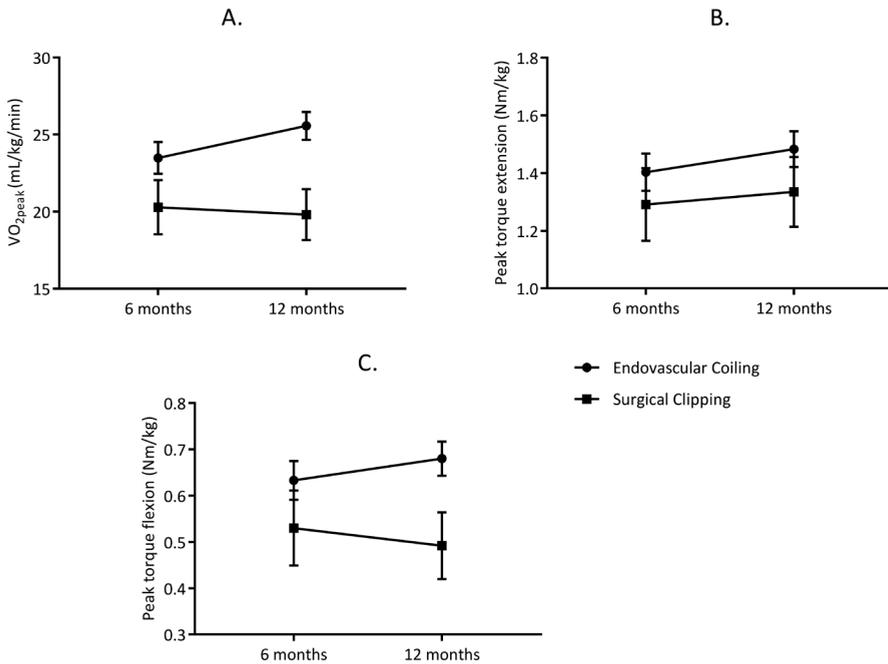
Linear mixed models	$\dot{V}O_{2peak}$ (n=43)			$PT_{ext}$ (n=48)			$PT_{flex}$ (n=48)		
	$\beta^{\dagger}$	95% CI for $\beta$	p-value	$\beta^{\dagger}$	95% CI for $\beta$	p-value	$\beta^{\dagger}$	95% CI for $\beta$	p-value
Time	+1.417	0.170 to 2.664	0.027	+0.071	-0.004 to 0.146	0.061	+0.026	-0.022 to 0.073	0.281
Sex	+6.606	3.062 to 10.150	0.001*	+0.340	0.120 to 0.561	0.003*	+0.214	0.075 to 0.353	0.003*
Age	-0.160	-0.295 to -0.025	0.021	-0.012	-0.020 to -0.003	0.010	-0.009	-0.015 to -0.004	0.002*
<b>Activities and functioning</b>									
Physical activity	+0.638	0.193 to 1.082	0.006	+0.023	-0.009 to 0.056	0.147	+0.018	0.001 to 0.036	0.037
Sedentary behavior	-0.030	-0.201 to 0.142	0.726	-0.004	-0.013 to 0.006	0.459	-0.002	-0.004 to 0.008	0.556
FIM+FAM	+0.469	-1.031 to 1.969	0.531	+0.125	0.041 to 0.209	0.004*	+0.057	0.002 to 0.112	0.042
<b>Baseline characteristics</b>									
GCS-score	+0.103	-0.708 to 0.914	0.799	+0.037	-0.010 to 0.084	0.116	+0.022	-0.008 to 0.053	0.146
Location aneurysm	+1.191	-2.059 to 4.441	0.463	+0.105	-0.101 to 0.310	0.311	+0.048	-0.082 to 0.179	0.459
Treatment	-4.946	-8.528 to -1.365	0.008	-0.135	-0.396 to -0.126	0.302	-0.176	-0.333 to -0.018	0.029
Pituitary dysfunction	-1.312	-4.531 to 1.908	0.415	-0.009	-0.216 to 0.197	0.928	-0.066	-0.195 to 0.063	0.306

Note: Each determinant was included in a separate linear mixed model with adjustment for sex (0=female, 1=male) and age (years).

Abbreviations: Time (0=6 months, 1=12 months); Physical activity (%24hrs); Sedentary behaviour (%waking hrs); FIM+FAM (range: 1-7); GCS-score (range: 1-15); Location aneurysm (0=anterior, 1=posterior); Treatment (0=coiling, 1=clipping); Pituitary dysfunction (0=no, 1=yes); CI, confidence interval;  $\dot{V}O_{2peak}$ , peak oxygen uptake ( $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ); GCS-score, Glasgow Coma Scale- score.

<sup>†</sup>Estimated  $\beta$ -coefficients;

\*Significant predictor of physical fitness after Bonferroni correction:  $p=0.05/10=0.005$ .



**Figure 4.** Graphic presentation of the estimated mean(SE) for  $\dot{V}O_{2peak}$  (A.), peak torque extension (B.) and peak torque flexion (C.) at six and twelve months specified for patients who underwent surgical clipping or endovascular coiling. Surgical clipping was negatively associated with  $\dot{V}O_{2peak}$  ( $p=0.008$ ) (A.) and peak torque flexion ( $p=0.029$ ) (C.).

The estimated  $\beta$ -coefficients from the models are presented in Table 3 and reflect the change in fitness that is associated with a one-unit change in the predictor. In this example we lighten the finding that patients who were physically more active had higher  $\dot{V}O_{2peak}$  (estimated  $\beta=0.638 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ); patients with +1% higher PA have a higher  $\dot{V}O_{2peak}$  of  $+0.638 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ . This finding indicates that 3.1% higher physical activity (45 min/24h) is associated with  $2.0 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  higher  $\dot{V}O_{2peak}$ .

## DISCUSSION

This one-year follow-up study showed that patients with a-SAH have low physical fitness over the first year.<sup>27, 31</sup> More than one-third of the patients had  $\dot{V}O_{2peak}$  values that were considered 'very low' at both six and twelve months post onset. Patients who were physically more active had higher levels of physical fitness, whereas patients with lower functional outcome had lower physical fitness. Further, patients who had been treated with surgical clipping are at risk of low physical fitness. Our findings indicate

that exercise interventions are warranted. Such intervention should involve both cardiorespiratory endurance and muscle strengthening components and should consider the promotion of PA. Further, these interventions should target patients with impaired functional outcome or those who had been treated with surgical clipping.

The applied treatment procedure to close the aneurysm was found to be a predictor of physical fitness. The  $\dot{V}O_{2\text{peak}}$  of patients who had been treated with surgical clipping was 22% lower compared to those who underwent endovascular coiling; this was 29% for knee flexor strength. Our findings indicate that endovascular coiling favors surgical clipping which is in line with a recent meta-analysis that showed that endovascular coiling yields optimal clinical outcome compared to surgical clipping.<sup>33</sup> Professionals should be aware of the fact that patients who had been treated with surgical clipping are at risk of low physical fitness. This finding may help to target future interventions in patients with a-SAH.

Physical activity has been related to improved physical fitness across different patient groups (e.g. coronary heart disease, diabetes mellites, obesity and stroke).<sup>8, 34</sup> In our sample we also found that patients who were physically more active had higher  $\dot{V}O_{2\text{peak}}$ . The estimated  $\beta$ -coefficients revealed that patients with higher PA (45 mins per 24h) have a  $2.0 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  higher  $\dot{V}O_{2\text{peak}}$  (reflects criterion improvement in stroke).<sup>30</sup> Future intervention studies are warranted to investigate whether higher levels of PA improve  $\dot{V}O_{2\text{peak}}$  in patients with a-SAH. Since PA in our study is based on total PA time, regardless intensity of activities, this means that walking or household activities are already associated with higher  $\dot{V}O_{2\text{peak}}$ . However, from research in sports and exercise we know that the intensity of PA plays a decisive role in fitness.<sup>6, 14</sup> Future studies are warranted to investigate optimal treatment paradigms to improve fitness in patients with a-SAH.

All longitudinal models were corrected for sex and age. According to the estimated  $\beta$ -coefficients, female sex and higher age were negatively associated with physical fitness. However, the finding that  $\dot{V}O_{2\text{peak}}$  in women was approximately 28% lower than in men, and the fact that  $\dot{V}O_{2\text{peak}}$  decreased 8% per 10-years of age are similar to findings in the general population.<sup>35, 36</sup>

Studies in patients with non a-SAH stroke, showed that exercise training can improve the cardiorespiratory fitness by 9-23%.<sup>37</sup> Furthermore, exercise training can reduce depressive symptoms, prevent complications associated with physical inactivity, and decrease the likelihood of recurrent stroke.<sup>14, 38</sup> There may be important health benefits from exercise training for patients with a-SAH as well. However, exercise interventions are lacking in a-SAH. Future intervention studies are warranted to investigate the beneficial effects of exercise training in patients with a-SAH.

Previous studies have already shown that cognitive impairments and psychological factors, such as mood and anxiety, lowers functional outcome after a-SAH.<sup>3</sup> In this study we provide evidence for an association between physical capacity and functional outcome. Our results revealed that FIM+FAM-scores were associated to knee flexion and extension strength, indicating that patients with lower muscle strength had lower functional outcome. From ageing studies, we know that improved knee muscle strength contributes to independent daily functioning.<sup>39</sup> It could be argued that improved knee muscle strength may also improve functional outcome in a-SAH. Future intervention studies are warranted to investigate whether strengthening exercise improves daily functioning after a-SAH.

The observed deficits in physical fitness (18% to 28% lower than reference) were smaller compared to patients with other types of stroke; where fitness parameters were 13% to 75% lower than healthy controls.<sup>10, 11</sup> This may be explained by the fact that patients with ischemic or hemorrhagic stroke are often more disabled due to focal brain damage and neuro-motor lesions, and therefore, less likely to maintain active lifestyles. Deficits in our group are comparable to patients with transient ischemic attack (TIA) and patients with minor ischemic stroke types (21% to 35% lower than controls).<sup>13, 40</sup>

Most interventions in stroke-rehabilitation are developed for patients with substantial functional disabilities, and therefore, predominantly focused on improving the performance of activities in daily living.<sup>14</sup> As a result, there are no appropriate exercise interventions for patients with minor disability after stroke.<sup>38</sup> Our findings indicate that exercise interventions in a-SAH should involve both cardiorespiratory endurance and strengthening exercise components. Interval training may be advantageous in a-SAH, to challenge the cardiorespiratory system without exhausting the muscular system.<sup>14</sup> Further, since we found a positive relationship between PA and physical fitness, future exercise programs may consider the promotion of daily PA in patients with a-SAH.

### **Limitations**

Some critical reflections are warranted. First, not all measurements were available for all patients. However, the data of most patients could be included in the final analyses by estimating the mean outcome using linear mixed model analyses. This statistical method takes into account the covariance between measurements within patients. Second, we could not confirm causality between parameters. However, the longitudinal relationships provide important clinical information about co-existence of problems which may help to direct therapeutic options in a-SAH. Ideal a CPET practice trial should have been implemented because practice effects of CPET may lead to improvements in CPET performance. However, implementing an additional practice trial was not feasible

within our study. Finally, selection bias may have occurred towards patients who are interested in sports and exercise which may have led to an underestimation of physical fitness deficits. However, participants did not differ from those who did not participated in HIPS-Rehab but were included in HIPS.

## **CONCLUSIONS**

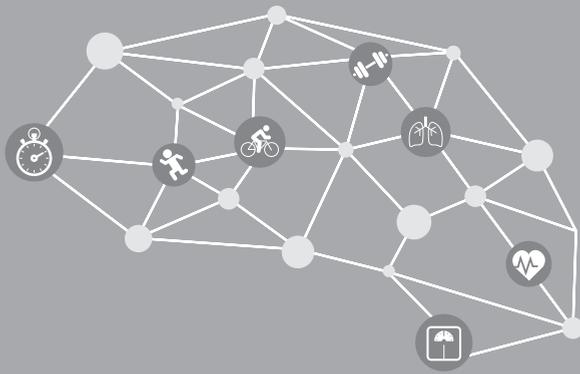
In summary, physical fitness remained low over the first year after a-SAH. More than one-third of the patients had 'very low' levels of  $\dot{V}O_{2peak}$  at six and twelve months post onset. Our findings revealed that patients who were physically more active had higher levels of physical fitness, whereas patients with impaired functional outcome had lower physical fitness. Further, patients who had been treated with surgical clipping are at risk of low physical fitness. Exercise interventions are warranted and may consider the promotion of daily PA and should target patients with impaired functional outcome or those who had been treated with surgical clipping. Future research is warranted to investigate whether rehabilitation services can adapt their programs for patients with a-SAH in order to meet the needs of these patients.

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# CHAPTER 7

**Fatigue after aneurysmal subarachnoid hemorrhage is highly prevalent and related to low physical fitness: a one year follow-up study.**

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[Submitted]

## ABSTRACT

**Objective:** To investigate whether low physical fitness and inactive and sedentary lifestyles play a role in the severity of fatigue in patients with an aneurysmal subarachnoid hemorrhage (a-SAH).

**Design:** Prospective one-year follow-up study.

**Setting:** University Medical Center.

**Participants:** A total of 52 patients with aneurysmal subarachnoid hemorrhage.

**Intervention:** Not applicable.

**Main Outcome Measures:** The Fatigue Severity Scale (FSS)-score, peak oxygen uptake ( $\dot{V}O_{2\text{peak}}$ ), isokinetic knee muscle strength (peak torque), physical activity (%24h period) and sedentary behavior (% waking hours) were evaluated at six and twelve months post onset.

**Results:** Fatigue was highly prevalent in the first year, and reported by 48% of the patients at six months and by 52% at twelve months post onset. The severity of fatigue did not change over follow-up time ( $p=0.876$ ). Fatigue was predicted by isokinetic knee extension (95%CI: -2.878 to -0.960;  $p<0.001$ ) and flexion strength (95%CI: -4.562 to -1.615;  $p<0.001$ ). A non-significant trend for a relationship was found between fatigue and  $\dot{V}O_{2\text{peak}}$  (95%CI: -0.149 to 0.009;  $p=0.079$ ). No relationships were found between fatigue and physical activity or sedentary behavior. Further, fatigue could not be predicted by disease-related characteristics.

**Conclusions:** Half of the patients were fatigued in the first year after a-SAH. Patients with lower physical fitness seem to be more severely fatigued. Interventions are necessary to reduce fatigue, and should consider exercise training as potential contributor to a multimodal treatment, preventing debilitating conditions in patients with a-SAH.

## INTRODUCTION

Aneurysmal subarachnoid hemorrhage (a-SAH) is characterized by the extravasation of blood into the subarachnoid space and is caused by a spontaneous rupture of an intracranial aneurysm.<sup>1</sup> Fatigue is the most frequently reported complaint, and may be present up to seven years post a-SAH.<sup>2</sup> Fatigue impacts the quality of life after a-SAH,<sup>2</sup> and is a strong predictor of death in patients with stroke.<sup>3</sup> Fatigue is a multifactorial construct, involving both psychological and biological factors.<sup>4</sup> Studies in patients with a-SAH found associations between fatigue and sleep disturbances, anxiety, depression, post-traumatic stress, and cognitive impairment.<sup>2</sup> However, these factors could not explain all cases of fatigue, and today, the underlying mechanisms remain unclear.

In patients with chronic conditions, fatigue has been associated with physical deconditioning, triggered by physical inactive and sedentary lifestyles.<sup>5, 6</sup> Fatigue can easily lead to the avoidance of daily activities, and subsequent reductions in physical fitness. Because fatigue plays an overwhelming role in daily life of most patients with a-SAH,<sup>2</sup> relationships between fatigue, physical fitness, physical activity (PA) and sedentary behavior (SB) are worth-investigating. In a recent cross-sectional study, we have found that patients with lower knee muscle strength seemed to be more severely fatigued.<sup>7</sup> However, longitudinal studies on fatigue and physical deconditioning are lacking. Insights in the longitudinal relationships between fatigue, physical fitness, PA and SB will give important clinical information which could help to improve rehabilitation and prevent debilitating conditions in patients with a-SAH.

Another important step in the prevention of fatigue is the identification of subgroups at higher risk of fatigue. Previous studies showed that the following disease-related characteristics interact with the long-term health outcomes after a-SAH: the applied treatment procedure, location of the aneurysm, presence of pituitary dysfunction and the severity of a-SAH.<sup>2, 8, 9</sup> In this study we additionally evaluate whether these characteristics are predictive of fatigue. The identification of sub-groups at increased risk of fatigue may help to direct future interventions.

The primary aim of this study was to investigate whether physical deconditioning, as presented by low physical fitness and physical inactive and sedentary lifestyles, play a role in fatigue after a-SAH. Secondary, we have evaluated whether fatigue could be predicted by disease-related characteristics. In this prospective follow-up, repeated measures of fatigue, physical fitness, PA and SB were analyzed at six and twelve months post onset. Findings from this study provide important clinical information to improve rehabilitation, and direct future interventions.

## METHODS

### Study Design, Setting and Participants

HIPS-Rehab is a prospective cohort study and part of the 'Hypopituitarism In Patients after Subarachnoid hemorrhage (HIPS) study'.<sup>8</sup> Individuals (aged  $\geq 18$  years) admitted to the department of Neurology of the Erasmus University Medical Center in Rotterdam between June 2009 and June 2012 were eligible for inclusion when they were diagnosed with a-SAH that was confirmed by computerized tomography (CT) of the brain, or in cases with negative CT by lumbar puncture. Exclusion criteria were: (I) hypothalamic or pituitary disease diagnosed prior to a-SAH, (II) history of cranial irradiation, (III) trauma capitis prior to a-SAH, (IV) other intracranial lesion apart from a-SAH, or (V) other medical or psychiatric condition or laboratory abnormality that may interfere with the outcome of this study. Measurements were performed at six and twelve months post onset. The study was approved by the Medical Ethics Committee of the Erasmus University Medical Centre. All participants provided written informed consent.

### Outcome measures

#### *Fatigue*

Fatigue was assessed by using the Dutch version of the Fatigue Severity Scale (FSS).<sup>10</sup> The FSS is a nine-item, self-administered questionnaire with scores ranging from 1 (strongly disagree) to 7 (strongly agree). The mean score of the nine items ranges from 1 (no signs of fatigue) to 7 (most disabling fatigue). Fatigue is defined a mean score of more than one standard deviation (SD) above the mean score for healthy individuals (FSS-score  $\geq 4.0$ ), and severe fatigue as a mean score of at least two SDs above the mean score in healthy individuals (FSS-score  $\geq 5.1$ ).<sup>11</sup> Internal consistency, reliability and validity of the FSS have been established in several patient groups, including stroke.<sup>10,11</sup>

#### *Physical Fitness*

Physical fitness was determined by evaluating the cardiorespiratory fitness and isokinetic knee muscle strength.<sup>12</sup> Before exercise testing, participants completed the Physical Activity Readiness Questionnaire and were screened for medical contraindications.<sup>13</sup> If there was any suspicion of an underlying cardiopulmonary pathology, exercise testing was not carried out. Patients with absolute contraindications were not excluded because they were still able to complete the FSS-questionnaire or perform activity monitoring measurement.

The cardiorespiratory fitness was determined by progressive cardiopulmonary exercise testing (CPET) on an electronically braked cycle ergometer (Jaeger ER800, Breda, The

Netherlands). CPET started with a 4-minute warm-up without resistance. Hereafter, the resistance increased automatically every 10 seconds and varied by sex (women: 12W/min; men: 16W/min) to ensure that voluntary exhaustion was reached within 8-14 minutes. CPET stopped when the participants stopped due to exhaustion or when they were unable to maintain target pedal rate (60-70 revolutions per minute). CPET could also be terminated because of medical complications, as described in the American College of Sports Medicine (ACSM)-guidelines.<sup>14</sup> Indirect calorimetry was performed using a breath-by-breath analyzing system (Oxycon Pro, Houten, The Netherlands). The cardiorespiratory fitness was defined as the highest mean peak value oxygen uptake  $\dot{V}O_{2peak}$  during 30 seconds of exercise, and was expressed in  $\dot{V}O_{2peak}$  per kilogram body mass ( $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ).

The following criteria were used to determine maximal physical exertion:  $\text{RER} > 1.0$  or  $\text{HR}_{peak}$  within 10 beats/min of the age predicted maximum heart rate ( $\text{HR}_{max}$ ); predicted by the following formula:

$$\text{HR}_{max} = 208 - (0.7 * \text{age})$$

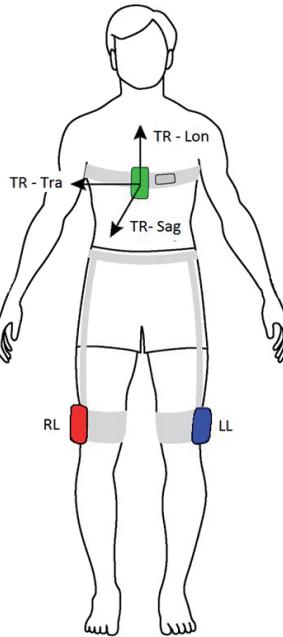
As beta-blocker medication reduces  $\text{HR}_{max}$  by approximately 25-30%,<sup>15, 16</sup> we adjusted the formula for participants with beta-blocker medication:

$$\text{HR}_{max} = 0.70 * [208 - (0.7 * \text{age})]$$

The peak torque (PT) of the knee extensors ( $\text{PT}_{ext}$ ) and flexors ( $\text{PT}_{flex}$ ) was determined by isokinetic dynamometry using the Biodex Dynamometer (Biodex, New York, USA). To minimise body movements, an adjustable seatbelt was applied across the chest, hip and thigh. The lateral femoral epicondyle was aligned with the rotational axis of the dynamometer. The test protocol involved 5 maximal knee extension and flexion contractions at  $60^\circ/\text{s}$ .<sup>17</sup> Muscle strength was recorded in torque (Nm) and corrected for body mass ( $\text{Nm}\cdot\text{kg}^{-1}$ ). PT was considered the maximum torque generated throughout one series of repetitions. Since there was no difference in PT between the left and right lower limb, we used the average PT of both limbs.

#### *Physical activity and sedentary behavior*

Physical activity (PA) and sedentary behavior (SB) were evaluated using an accelerometer-based activity monitor (VitaMove, Veldhoven, The Netherlands; Figure 1). This monitor consists of three recorders which are wirelessly connected and synchronized every 10 seconds. Each recorder has its' own accelerometer (Freescale MMA7260Q, Denver, USA).<sup>18</sup> The VitaMove has demonstrated validity for quantifying body postures



**Figure 1.** Placement of the VitaMove activity monitor.

Abbreviations: TR, trunk sensor; RL, right leg sensor; LL, left leg sensor; Lon=longitudinal axis; Sag=sagittal axis; Tra=transversal axis

and movements in healthy subjects and different patient populations.<sup>18, 19</sup> Participants wore the VitaMove on weekdays, except during swimming, bathing and sleeping. The intended duration of measurement was three consecutive days with a minimum of one day.<sup>20, 21</sup> Participants were instructed to continue their ordinary daily activities. To avoid measurement bias, principles of measurement were explained afterwards. Participants kept activity diaries to report reasons of non-wear periods. Kinematic analysis were performed using VitaScore Software (VitaScore BV, Gemert, The Netherlands).<sup>18</sup> The following outcome measures were determined as the mean of available measurement days: duration of PA as percentage of 24-hrs (including walking, cycling, running, and non-cyclic movements), and duration of SB as a percentage of waking hours (including lying and sitting activities).

### *Characteristics*

The following disease-related characteristics were collected at hospital intake: severity of a-SAH as determined by the Glasgow Coma Scale (GCS)-score,<sup>22</sup> location aneurysm (anterior vs. posterior circulation), treatment procedure (surgical clipping vs. endovascular coiling), presence of complications (re-bleed, delayed cerebral ischemia, hyponatremia, and hydrocephalus) and pituitary dysfunction.

## Statistical analyses

All data are expressed as mean (SD) unless otherwise indicated. Differences between participants and nonparticipants were verified with independent t-tests for interval variables and  $\chi^2$ -tests for categorical variables. Parametric tests were applied because Shapiro-Wilk-tests showed that the data for fatigue was normally distributed. McNemar-test of symmetry was selected to analyze the difference in individual classification of fatigue (no fatigue, fatigue, severe fatigue) between six and twelve months.

Linear mixed models were used to study changes in the estimated mean FSS-score,  $\dot{V}O_{2\text{peak}}$ ,  $PT_{\text{extr}}$ ,  $PT_{\text{flex}}$ , PA and SB over follow-up time. Time (follow-up visit) was entered as predictor of the dependent outcome. Linear mixed models are flexible in handling missing values because it takes into account the covariance between measurements within patients. Time-dependent relationships between the severity of fatigue (FSS-score) and one of the following factors were analyzed:  $\dot{V}O_{2\text{peak}}$ ,  $PT_{\text{extr}}$ ,  $PT_{\text{flex}}$ , PA and SB. The following fixed factors were entered to investigate whether disease-related characteristics can predict fatigue: GCS-score, location aneurysm, treatment, complications and pituitary dysfunction. Separate models were created for each covariate.

All models were adjusted for sex and age to correct for possible confounding effects. Statistically, sex and age were not always significant confounders, but were kept in each model because they are considered confounding in the analyses of fatigue, physical fitness, PA and SB.<sup>23</sup> Considering the sample size (n=52), we allowed a maximum of three factors in each model to maintain sufficient statistical power. We reported the estimated  $\beta$ -coefficients, 95% confidence intervals and p-values. The significance level was set at  $p < 0.05$  (SPSS Inc, Chicago, IL). Bonferroni correction was applied to adjust for type I error for multiple comparisons.

## RESULTS

### Study population

A total of 241 patients were admitted to the Intensive Care Unit with a diagnosis of a-SAH. Of the 84 eligible patients, 52 participated in HIPS-Rehab (Table 1). There were no significant differences between participants (n=52) and non-participants (n=32) with respect to: sex ( $p=0.291$ ), age ( $p=0.996$ ), GCS-score ( $p=0.136$ ), treatment ( $p=0.489$ ) and location of the aneurysm ( $p=0.469$ ).

Figure 2 presents a detailed flow diagram of measurements included in the final analyses. Not all measurements could be included from all patients. CPET data of 43 patients

**Table 1.** Patient characteristics.

Characteristics	Patients with a-SAH (n=52)
Age (years), mean (SD)	56.1 (13.5)
Sex (men), n (%)	16 (31)
GCS-score, mean (SD)	13.5 (2.1)
Location aneurysm, n(%)	
- Anterior	31 (60)
- Posterior	21 (40)
Treatment procedure, n(%)	
- Endovascular coiling	47 (79)
- Surgical clipping	11 (21)
Secondary complications, n(%)	
- Re-bleed	0 (-)
- Delayed cerebral ischemia	7 (13)
- Hyponatremia	6 (12)
- Hydrocephalus	13 (25)
Pituitary dysfunction, yes (n%)	24 (46)

Abbreviations: GCS-score, Glasgow Coma Scale-score

were included (83% of the sample). In total, six patients could not perform CPET because of contraindications (n=3), for logistical reasons (n=2) and one patient had a back injury (n=1). Further, three measurements were excluded because of not meeting the criteria of maximal physical exertion. Isokinetic dynamometry data of 48 patients were included (92%); three patients could not perform maximal isokinetic dynamometry because of medical reasons and one because of logistical reason. Activity-monitoring data of 44 participants were included (85%); measurements in four patients were lost due to technical failure, three because of logistical reasons and one patient refused measurement.

### Longitudinal evaluation

Table 2 presents detailed information about the change in the estimated mean FSS-score,  $\dot{V}O_{2peak}$ ,  $PT_{extr}$ ,  $PT_{flexr}$ , PA and SB over follow-up time. The estimated mean FSS-score did not change, and also the proportion of patients that reported fatigue remained stable with 48% at six months and 52% at twelve months ( $p=0.678$ ). The estimated mean  $\dot{V}O_{2peak}$  significantly increased over time (+6.2%;  $p=0.027$ ), there was a nonsignificant trend for an increase in  $PT_{ext}$  (+5.1%;  $p=0.061$ ), whereas the  $PT_{flex}$  did not change (+4.9%,  $p=0.281$ ). The estimated mean physical activity time remained stable, and was 7.06% (SE 0.48) at six months and 6.64% (SE 0.55) at twelve months ( $p=0.341$ ), representing 102 and 96 min per 24h, respectively. The estimated mean sedentary time did also not change, and was 63.55% (SE 2.65) at six months and 62.88% (SE 2.55) at twelve months, representing 8.38h and 8.45h, respectively.

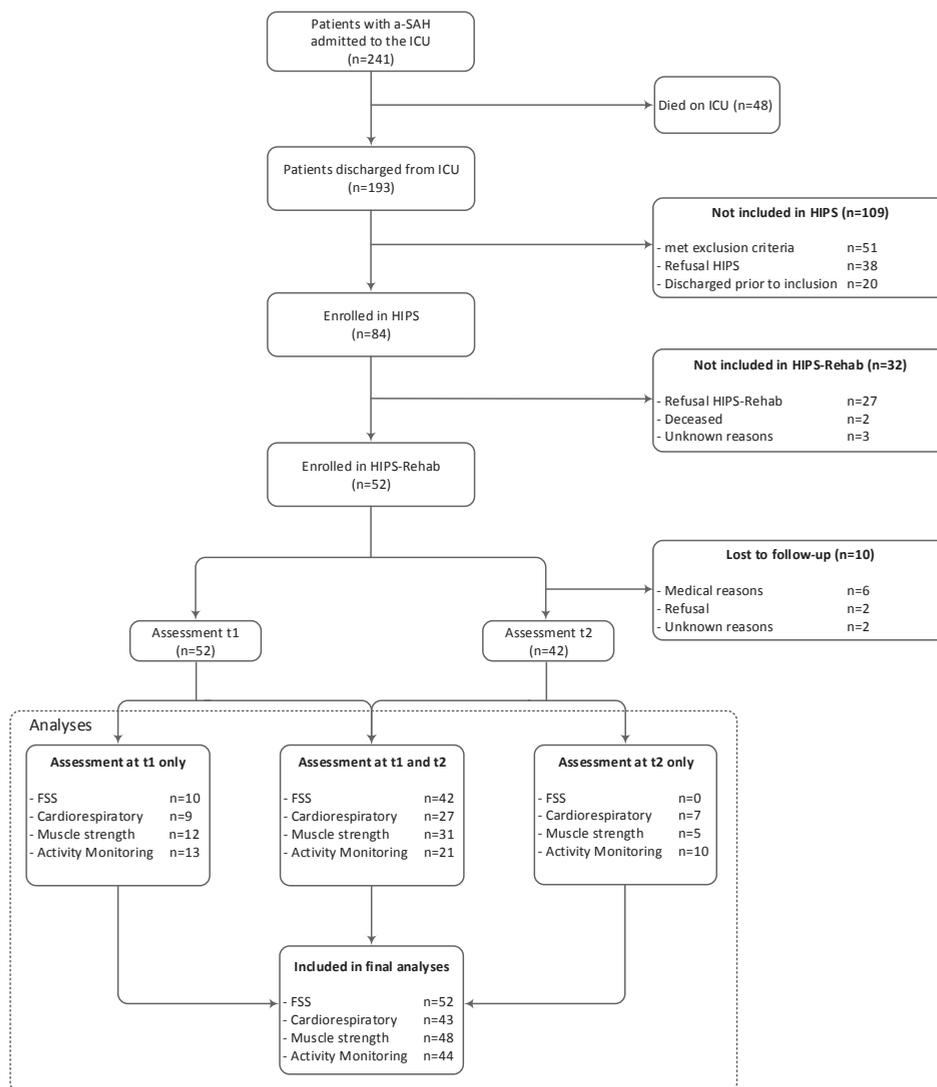


Figure 2. Flow diagram.

Table 3 presents the individual classifications of fatigue over follow-up time. The proportion of patients reporting ‘severe fatigue’ (FSS-score $\geq$ 5.1), ‘fatigue’ ( $4.0\geq$ FSS-score $<$ 5.1), and ‘no fatigue’ (FSS-score $<$ 4.0) was at six months 23.8%, 28.6%, and 47.6%, respectively. At twelve months, levels were reported as 26.2%, 26.2%, and 47.6%, respectively. Individual classifications of fatigue did not change over time ( $p=0.837$ ).

**Table 2.** Estimated Mean (SE) values of fatigue, physical fitness, physical activity and sedentary behavior, with significance level of change over time.

	6 months (t1)	12 months (t2)	$\Delta$ t1-t2 <sup>#</sup>	95% CI for $\Delta$	p-value
<b>Fatigue</b>					
FSS-score	3.60 (0.24)	3.63 (0.25)	+0.026	-0.36 to 0.31	0.876
<b>Cardiorespiratory fitness</b>					
$\dot{V}O_{2peak}$ (mL·kg <sup>-1</sup> ·min <sup>-1</sup> )	22.79 (0.94)	24.20 (0.91)	+1.417	0.170 to 2.664	0.027
<b>Knee muscle strength</b>					
PT <sub>ext</sub> (Nm·kg <sup>-1</sup> )	1.38 (0.06)	1.45 (0.06)	+0.071	-0.004 to 0.146	0.061 <sup>‡</sup>
PT <sub>flex</sub> (Nm·kg <sup>-1</sup> )	0.61 (0.04)	0.64 (0.04)	+0.026	-0.022 to 0.073	0.281
<b>Activities</b>					
PA (%24h)	7.06% (0.48)	6.64% (0.55)	-0.412	-0.461 to 1.284	0.341
SB (%waking)	63.55% (2.65)	62.88% (2.55)	-0.674	-3.342 to 4.691	0.732

Abbreviations: CI, confidence interval; FSS-score, Fatigue Severity Scale-score;  $\dot{V}O_{2peak}$ , peak oxygen uptake; PT<sub>ext</sub>, Peak torque extension; PT<sub>flex</sub>, Peak torque flexion; PA, Physical activity; SB, Sedentary behavior. Note: All models were adjusted for sex and age. <sup>‡</sup>Nonsignificant trend for a difference ( $p < 0.10$ ).

<sup>#</sup>Estimated mean difference (t1 -t2);

<sup>‡</sup>Nonsignificant trend for a difference ( $p < 0.10$ ).

**Table 3.** Distribution of fatigue at follow-up (n=42) by level of fatigue at six months.

Fatigue	n	%
Severe fatigue at six months (FSS-score $\geq 5.1$ )	10	23.8%
- Severe fatigue at twelve months	6	60.0%
- Fatigue at twelve months	3	30.0%
- No fatigue at twelve months	1	10.0%
Fatigue at six months ( $4.0 \geq$ FSS-score $< 5.1$ )	12	28.6%
- Severe fatigue at twelve months	2	16.7%
- Fatigue at twelve months	6	50.0%
- No fatigue at twelve months	4	33.3%
No fatigue at six months (FSS $< 4.0$ )	20	47.6%
- Severe fatigue at twelve months	3	15.0%
- Fatigue at twelve months	2	10.0%
- No fatigue at twelve months	15	75.0%

Abbreviations: FSS, Fatigue Severity Scale.

### Determinants of fatigue

Table 4 presents detailed information about the mixed models that estimated the severity of fatigue. The PT<sub>ext</sub> and PT<sub>flex</sub> were both related to fatigue ( $p < 0.001$ ). Furthermore, there was a nonsignificant trend for a relationship between  $\dot{V}O_{2peak}$  and fatigue ( $p = 0.079$ ). These findings indicate that patients with lower physical fitness were more

**Table 4.** Determinants of fatigue; linear mixed models with fatigue as dependent variable and physical fitness, physical activity, sedentary behavior and disease-related characteristics as independent variables.

Linear mixed models	FSS-score			
	F	$\beta^{\dagger}$	95% CI for $\beta$	p-value
Time, n=52	0.025	+ 0.026	-0.358 to 0.306	0.876
<b>Aerobic capacity</b>				
VO <sub>2peak</sub> (mL·kg <sup>-1</sup> ·min <sup>-1</sup> )	3.201	- 0.070	-0.149 to 0.009	0.079 <sup>‡</sup>
<b>Knee muscle strength</b>				
Peak torque extension (Nm·kg <sup>-1</sup> )	15.954	- 1.918	-2.878 to -0.960	<0.001 <sup>*</sup>
Peak torque flexion (Nm·kg <sup>-1</sup> )	17.481	- 3.089	-4.562 to -1.615	<0.001 <sup>*</sup>
<b>Activities</b>				
Physical activity	0.004	- 0.004	-0.144 to 0.135	0.952
Sedentary behavior	0.888	- 0.019	-0.060 to 0.022	0.350
<b>Characteristics</b>				
GCS-score	1.573	+ 0.125	-0.326 to 0.075	0.216
Location aneurysm	0.219	- 0.199	-1.056 to 0.658	0.642
Treatment procedure	0.111	- 0.177	-1.244 to 0.890	0.740
Complications	2.289	-0.623	-1.454 to 0.206	0.137
Pituitary dysfunction	1.966	-0.577	-1.405 to 0.251	0.168

Note: Each determinant was included in a separate linear mixed model with adjustment for sex (0=female, 1=male) and age. Time (0=6 months, 1=12 months); GCS-score (range: 1-15); Location aneurysm (0=anterior, 1=posterior); Treatment procedure (0=clipping, 1=coiling); Complications (0=no, 1=yes); Pituitary dysfunction (0=no, 1=yes).

Abbreviations: CI, confidence interval; FSS-score, Fatigue Severity Scale-score; VO<sub>2peak</sub>, peak oxygen uptake; GCS-score, Glasgow Coma Scale- score.

<sup>†</sup>Estimated  $\beta$ -coefficients;

<sup>\*</sup>Significant predictor of fatigue after Bonferroni correction:  $p=0.05/10=0.005$ ;

<sup>‡</sup>Nonsignificant trend for a relationship.

severely fatigued. There were no relationships between fatigue and PA or SB. Further, fatigue could not be predicted by disease-related characteristics.

The estimated  $\beta$ -coefficients from the models are presented in Table 4 and reflect the change in FSS-score that is associated with a one-unit change in the independent predictor. For example, a 20% higher knee flexion strength ( $=0.122 \text{ Nm}\cdot\text{kg}^{-1}$ ), is associated with a 0.4 points lower FSS-score ( $=11\%$  of the mean FSS-score).

## DISCUSSION

This is the first study to longitudinally evaluate whether physical deconditioning plays a role in fatigue after a-SAH. In this follow-up, we have evaluated objective measures

of physical fitness, PA and SB without bias from the subjective character of questionnaires.<sup>24,25</sup> Our findings revealed longitudinal relationships between physical fitness and fatigue, in that patients with lower knee muscle strength were more severely fatigued. Further, we found a nonsignificant trend for a relationship between the cardiorespiratory fitness and fatigue. Fatigue persisted over the first year and was reported by approximately half of the patients which is more than twice as high compared to the general population (18%).<sup>10,11</sup> As an extension to our cross-sectional findings, this study showed a more permanent character of fatigue and longitudinal relationships with physical fitness. Since fatigue complaints do not diminish over time, interventions are warranted. Future interventions should preferably incorporate exercise training to improve physical fitness which may provide a physical reserve to fatigue.

Patients with lower physical fitness were more severely fatigued. Although the cardiorespiratory fitness (+6.2%) and knee extensor strength (+5.2%) slightly improved over follow-up time, the severity of fatigue remained unchanged. Studies in stroke, showed that interventions can improve physical fitness up to 20%.<sup>26</sup> In our study a 20% higher level of physical fitness is associated with a 11% lower FSS-score. However, future intervention studies are warranted to investigate whether improvements in fitness would lead to reductions in fatigue. Although we do not assume that exercise training is the 'golden bullet' targeting fatigue, we rather suppose that it is an important contributor to a multimodal treatment. Moreover, exercise training is a well-known contributor to improved health status,<sup>27</sup> and may therefore, serve multiple goals in patients with a-SAH.

Relationships between fatigue and physical fitness have frequently been explained in the context of inactive and sedentary lifestyles.<sup>5</sup> Although patients have low levels of PA (102 min at six months and 96 min at twelve months) and high levels of SB (8.38h at six months and 8.45h at twelve months),<sup>24,28,29</sup> PA and SB were not related to fatigue. This indicates that the severity of fatigue did not interact with the volume of physical activities or sedentary time. It might be argued that other types of PA such as the amount of moderate to vigorous PA, are more indicative of fatigue as these types are physically more demanding. Further, the absence of such a relationship may also be explained by a compensation strategy in which patients lower their physical activities of increase sedentary time to conserve energy and prevent fatigue.

Interventions targeting fatigue have not been studied in patients with a-SAH. Studies in other patient populations have shown that self-management programs,<sup>30</sup> cognitive therapy and exercise training can reduce fatigue.<sup>31,32</sup> Further, in patients with stroke, the combination of cognitive therapy and graded exercise training was found to be more effective in the treatment of fatigue than stand-alone cognitive therapy.<sup>33</sup> This training

included walking on a treadmill, strengthening exercise, and homework assignments (2h sessions, twice a week).<sup>33</sup> If exercise training reduces fatigue after a-SAH, there are several putative mechanisms; exercise improves physical fitness and provides a physical reserve to fatigue; or exercise may support self-esteem, self-efficacy and social interactions, which may contribute to improved psychosocial well-being which in turn, may alleviate fatigue complaints.<sup>32</sup>

Previous studies in a-SAH suggested that disease-related characteristics, such as cerebral ischemia or hydrocephalus, can trigger fatigue because they can easily disrupt fronto-subcortical neuro-circuits which could lead to impairments in attention and arousal.<sup>4</sup> Further, pituitary dysfunction, with low basal cortisol levels and growth hormone deficiency, is another characteristic which can also trigger fatigue.<sup>2, 34</sup> However, we did not find evidence for a relationship between disease-related characteristics and fatigue which makes it difficult to identify sub-groups and direct future interventions.

### **Study limitations**

Some possible limitations should be discussed. First, a large proportion of women participated (69%). Therefore, we might have overestimated the prevalence of fatigue. For example, a study on fatigue in a-SAH that recruited predominantly women (82% of the sample),<sup>9</sup> showed a higher frequency of fatigue than a study that included roughly equal number of men and women.<sup>35</sup> The large proportion of women in this sample can be explained by the fact that women have a higher risk of a-SAH than men; the incidence of a-SAH in the Netherlands for women is 11.2 per 100,000 persons per year whereas for men this is 7.6 per 100,000 persons per year.<sup>36</sup> Further, not all measurements were available from all patients. However, mixed model analyses allowed us to include patients in the analyses for who some of the data is missing. This statistical approach takes into account the covariance between measurements within patients, and allowed us to make full use of the data. Third, the sample size (n=52) allowed us to include a maximum of three factors in each model. Therefore, we were not able to study interaction terms. Finally, we have to take in consideration that our study does not include data about pre-existing fatigue, prior to a-SAH.

### **CONCLUSIONS**

In summary, half of the patients had fatigue complaints in the first year after a-SAH. Patients with lower knee muscle strength were more severely fatigued, while there was a trend for a relationship between the cardiorespiratory fitness and fatigue. We did not find evidence for a relationship between fatigue and PA or SB. Further, fatigue could

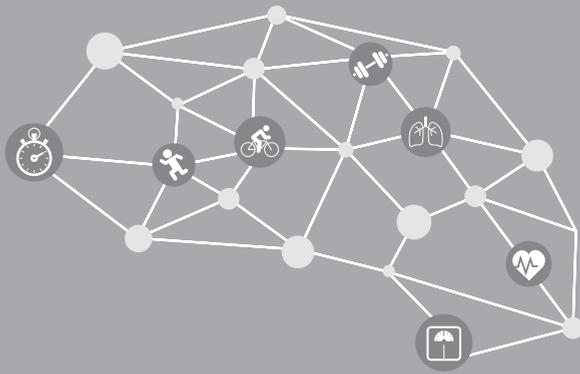
not be predicted by disease-related characteristics. According to our findings, higher physical fitness may provide a physical reserve to fatigue in patients with a-SAH. Future intervention studies are warranted to investigate the beneficial effects of exercise training in patients with a-SAH.

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# CHAPTER 8

## General Discussion



The health benefits of physical fitness and physical active lifestyles are numerous. Higher levels of fitness and activity have been associated with lower all-cause mortality, and the prevention of chronic diseases such as hypertension, diabetes, cancer and obesity.<sup>1-5</sup> In contrast, sedentary behavior negatively impacts cardiovascular health, independent of the amount of physical activity.<sup>6-8</sup> Patients with aneurysmal subarachnoid hemorrhage (a-SAH) may be at risk of low fitness, and inactive and sedentary lifestyles because fatigue plays an overwhelming role in daily life of most patients.<sup>9</sup> Physically inactive and sedentary lifestyles can lead to physical deconditioning (i.e. a vicious circle of fatigue, inactivity and low fitness). Studies on physical fitness, physical activity, and sedentary behavior are lacking in a-SAH. This may be due to the fact that it is assumed that most a-SAH survivors have a favorable outcome, and therefore they have frequently been excluded from stroke rehabilitation research. Insights in the levels of physical fitness, physical activity, and sedentary behavior may contribute in understanding the consequences of a-SAH and in improving rehabilitation programs.

The primary aim of this thesis is to evaluate physical fitness, physical activity and sedentary behavior in the first year after a-SAH. Fitness parameters and activity profiles at six months are compared to that of sex- and age-matched controls. Further, changes in fitness, activity, and sedentary behavior are evaluated between six and twelve months. Secondary, we have studied whether physical fitness, physical activity and sedentary behavior relate to the severity of fatigue. Further, we wanted to evaluate whether we could predict subgroups at risk of poor outcomes, which may help to direct future interventions. Since fatigue plays an overwhelming role in daily life of most patients, we have hypothesized that patients with a-SAH have impaired physical fitness, and predisposed to physically inactive and sedentary lifestyles. This chapter concerns our main findings and interpretation within the context of the published literature. Finally, this chapter addresses methodological considerations, recommendations for future research and clinical implications.

## MAIN FINDINGS

A major finding of this thesis is that patients have considerably impaired physical fitness. The cardiorespiratory fitness and knee muscle strength were 22% to 40% lower compared to that of sex- and age-matched controls. Longitudinal evaluations showed only small improvements in fitness over follow-up time (significant increments were found up to 6.2%). However, all fitness parameters at twelve months remained lower than reference values.<sup>10</sup> In more than one-third of the patients, levels of cardiorespiratory fitness were 'very low' (according to the classification of the Cooper Institute),<sup>10</sup> which is associated with an increase in all-cause mortality.<sup>11</sup> Another major finding is that

patients with a-SAH have inactive and sedentary lifestyles. Patients were 25% less physically active compared to controls, and participated particularly less in cycling activities. Further, patients spent 8.5 hours sedentary during waking hours. Such high levels of sedentary time have been associated with a 7.5% increase in all-cause mortality.<sup>12</sup> Further, patients break their activity time into shorter periods, whereas uninterrupted periods of sedentary time last longer compared to controls, which is not favorable from a health perspective.<sup>13</sup>

In our sample, fatigue is reported by approximately half of the patients, and its severity did not diminish over follow-up time. Our findings reveal significant relationships between fitness and fatigue, and indicated that patients with lower knee muscle strength are more severely fatigued. We did not find evidence for a relationship between activity or sedentary behavior and fatigue. To direct future interventions, we have analyzed whether we could identify patients with high fatigue or poor physical fitness. In our sample, we found no significant relationships between patient characteristics and fatigue, but patients who had been treated with neurosurgical clipping have significantly lower physical fitness than those who underwent endovascular coiling.

This is the first study that applied maximal progressive exercise testing in patients with a-SAH. Since no adverse events occurred, it seems that progressive exercise testing can be safely applied in patients with a-SAH after pre-test medical screening for absolute contra-indication to physical exercise.<sup>14, 15</sup> However, progressive cardiopulmonary exercise testing with gas-exchange analyses has limited availability in most rehabilitation facilities. Therefore, we have evaluated whether we could predict the cardiorespiratory fitness (peak oxygen uptake;  $\dot{V}O_{2\text{peak}}$ ) of patients with a-SAH by performing a submaximal six-minute walk test (6MWT). Our findings revealed that the 6MWT can be selected to estimate the mean  $\dot{V}O_{2\text{peak}}$  at an aggregated group level, but that the relatively large prediction error does not allow for an accurate prediction of  $\dot{V}O_{2\text{peak}}$  in individual patients.

## **INTERPRETATION AND CONTEXT IN THE LITERATURE**

Low fitness has been reported across different patient populations.<sup>2</sup> Within the scope of stroke, the observed fitness deficits in a-SAH are comparable to that of patients with transient ischemic attack (TIA) and patients with minor strokes. In these patients, fitness parameters were found to be 21% to 35% lower than in controls.<sup>16, 17</sup> In patients with more severe ischemic or hemorrhagic stroke types, fitness levels seem to be more impaired compared to patients with a-SAH, as fitness parameters in these patients were found to be up to 75% lower than in controls.<sup>18</sup> This difference may be explained by the

fact that patients with a-SAH seem to have a better functional outcome than patients with stroke. To illustrate, residual impairments such as hemiparesis or spasticity are common in ischemic or hemorrhagic stroke,<sup>19</sup> whereas these impairments are not observed in our sample. Therefore, from a functional perspective, patients with a-SAH are more likely to maintain active lifestyles, and preserve physical fitness compared to patients with stroke.<sup>20</sup> The fact that patients with a-SAH have low fitness deserves attention in clinical practice, especially because it is initially assumed that most survivors have a favorable outcome. When physical fitness becomes low, physical activities may either become limited or impossible to perform.<sup>21</sup>

In this thesis, we found that patients with a-SAH have lower physical activity levels compared to controls, which has been observed across different groups, including patients with stroke.<sup>2</sup> Patients with a-SAH spend 7.3% per 24h in physical activities, which is 25% less compared to controls, placing them at risk of poor health outcomes.<sup>1</sup> Patients with a-SAH seem to be less compromised in the performance of physical activities than patients with other types of stroke, where activity levels have been found to be 40% lower than in controls.<sup>22</sup> Longitudinal analyses showed that the amount of physical activity did not change over follow-up time. As discussed above, impairments such as hemiparesis or spasticity did not occur, so motor problems cannot explain low activity levels. Although we have hypothesized that fatigue may be related to inactive lifestyles, such relationship was not observed in our study. From studies in patients with chronic conditions we know that other factors play an important role in physical activity as well. For example, a lack of awareness of the beneficial health effects of active lifestyles, limited resources to promote physical activities, and a lack of structured support are associated with low physical activity levels.<sup>2, 23</sup> Furthermore, in a-SAH there may be other, more specific barriers for undertaking physical activity, as will be discussed below.

Previous literature in a-SAH shows that attentional deficits, passive coping styles, and anxiety limit the resumption of premorbid activities such as working and leisure activities.<sup>24-27</sup> It could be argued that these complaints also interact with the ability to undertake daily activities or exercise. For example, our findings reveal that patients participate particularly less in cycling activities, and because cycling requires increased levels of attention due to multitasking and traffic participation, attentional deficits in a-SAH may lead to the avoidance of cycling. Further, feelings of anxiety may arise from the life-threatening experience of the ruptured aneurysm (in both patients and relatives), and may limit confidence to undertake physical activities after coiling or clipping the aneurysm. Finally, low fitness causes elevated energy costs of movements. For example, the oxygen cost of walking in deconditioned patients is two times higher than in controls.<sup>28</sup> This phenomenon might explain why patients break their activity time into

shorter periods compared to controls. Shorter periods of activity may be indicative of a higher number of resting moments which may arise from increased fatigability.

Next to physical activity we have examined sedentary behavior. Patients were 8.5 hours sedentary during waking hours, which is associated with an increase of 7.5% in all-cause mortality.<sup>10</sup> Further, uninterrupted periods of sedentary behavior in patients lasted longer than in controls. Prolonged uninterrupted periods of sedentary time have been negatively associated with cardiovascular health.<sup>5,7</sup> Therefore, optimizing sedentary behavior, by reducing its' total volume and breaking uninterrupted periods, may present another challenge in a-SAH rehabilitation.

Fatigue is the most frequently reported complaint in a-SAH.<sup>9</sup> In our sample, half of the patients has fatigue complaints, which is more than twice as high compared to the general population (18%).<sup>29</sup> Further, fatigue complaints do not diminish over time. Our findings are in line with previous literature, showing high frequencies of persistent fatigue problems in a-SAH (31% to 91% up to seven years post onset).<sup>9</sup> Studies reported that different frequencies of fatigue at different time points may be explained by different mechanisms. For example, early fatigue (<1y after a-SAH) is thought to be related to the neuroendocrine or inflammatory changes (i.e. effect of blood on the cerebral cortex), whereas late fatigue complaints ( $\geq 1$ y after a-SAH) may be related with factors such as anxiety, depression, post-traumatic stress, memory problems, personality changes, sleep disturbances, cognitive and physical impairment.<sup>9</sup>

Durstine et al. hypothesized that fatigue, fitness, and activity interact, leading to a vicious circle of physical deconditioning.<sup>2</sup> In line with this, our findings showed that patients with lower knee muscle strength were more severely fatigued. Further, we found a non-significant trend for a relationship between the cardiorespiratory fitness and the severity of fatigue. Relationships between fitness and fatigue have been reported across different patient populations, including stroke.<sup>2, 30</sup> However, we did not find a relationship between activity or sedentary time and fatigue. This may be explained by the fact that patients may lower their physical activity, or increase their sedentary behavior, to conserve energy and prevent fatigue.

To direct future interventions in a-SAH, we have evaluated whether we could identify patients at risk of high fatigue or poor fitness. In our sample, we were not able to identify subgroups at risk of fatigue, but patients who had been treated with surgical clipping seem to have lower physical fitness than those who underwent endovascular coiling (fitness parameters were 22% to 29% lower in surgical clipping compared to endovascular coiling). This may be explained by the fact that the absolute risk of dependency

in the first year is higher in patients treated with surgical clipping and therefore, these patients may be less likely to preserve their fitness levels.<sup>31</sup> Our findings are in line with a meta-analysis showing that endovascular coiling yields a better clinical outcome than surgical clipping.<sup>32</sup>

This is the first study that applied progressive cardiopulmonary exercise testing (CPET) and maximal isokinetic dynamometry in patients with a-SAH. Therefore, we have implemented a supplementary safety protocol which matches the recommendations for conducting exercise testing in stroke,<sup>14</sup> and the guidelines of the American College of Sports Medicine.<sup>15</sup> No adverse events were observed during exercise testing in patients who were pre-screened for medical contraindications. However, progressive CPET with gas exchange analyses requires specialized knowledge and infrastructure, with limited availability in most rehabilitation facilities. Therefore, there seems to be a need for safe and valid submaximal alternatives to CPET. In searching for alternatives, we have evaluated whether we could predict  $\dot{V}O_{2\text{peak}}$  by performing a submaximal six minute walk test (6MWT). We found that the six minute walk distance (6MWD) is strongly related to  $\dot{V}O_{2\text{peak}}$ , indicating that the 6MWT can be selected to predict mean  $\dot{V}O_{2\text{peak}}$  at an aggregated group level. This is relevant for the evaluation of therapy programs and for research purposes. However, linear regression analyses show a large prediction error, representing 16% of mean  $\dot{V}O_{2\text{peak}}$ . Due to this large error, the 6MWT seems to be of limited value predicting  $\dot{V}O_{2\text{peak}}$  in individual patients. This finding is in line with studies in persons with cardiopulmonary disease and heart failure.<sup>33-35</sup>

## METHODOLOGICAL CONSIDERATIONS

This study is the first to evaluate physical fitness, physical activity and sedentary behavior in patients with a-SAH. Therefore, a major strength of this study is that it provides new insights in the consequences of a-SAH and offers important information for future research and treatment. Another strength is that we have evaluated objectively obtained measures of fitness, physical activity and sedentary behavior without bias from the subjective character of questionnaires. Subjective questionnaires have been found to overestimate fitness and activity levels, possibly due to social desirability bias.<sup>22, 36</sup> Furthermore, we have included sex- and age-matched controls, which has strengthened our study design. Patients and controls performed identical measurements, which enabled detailed interpretations of fitness parameters and activity profiles.

A critical note concerns the external validity of the study sample. Validity issues may arise when patients (or controls) are not representative of the underlying target popula-

tion. Explicit in- and exclusion criteria were defined to ensure a homogenous patient population. All patients were recruited from the Neurology department of a university hospital (Erasmus MC, Rotterdam, the Netherlands) between June 2009 and June 2012. We have identified 193 patients with a diagnosis of a-SAH and recognized a target population of 122 patients of whom 52 consented to participate (43%). Since baseline characteristics seem to be in line with previous literature on a-SAH, with respect to sex (69% women), age (mean age  $56\text{y} \pm 13.5\text{y}$ ), severity of a-SAH (18% poor grade a-SAH) and treatment procedure (79% endovascular coiling),<sup>37-39</sup> our sample seems representative of the underlying target population. Selection bias may, however, have occurred towards patients who are more interested in sports and exercise. As these patients are more likely to take part in physical activities, we may have overestimated fitness and activity levels of patients with a-SAH.

In an attempt to ensure comparability between patients and controls, patients were individually matched with a control subject based on sex and age ( $\pm 5$  years).<sup>40</sup> One could argue that adding additional matching criteria, such as level of education or social economic status, would have increased comparability between groups. However, for logistic reasons it was not feasible to match for multiple criteria. Another note concerns the generalizability of our control group. Because there are no appropriate reference values for fitness, activity and sedentary behavior for the Dutch population, it remains uncertain whether the control group is a representative of the underlying source population. However, the observed fitness levels in controls seem to be comparable to that of sex- and age-related reference values (non-Dutch),<sup>12, 41</sup> and physical activity profiles seem to be even somewhat lower, than results as measured with the same activity monitor, in other healthy comparison groups (9.7% vs. 10% to 12% per 24h).<sup>22, 42, 43</sup>

Although a sample size of 52 is relatively large considering the incidence of a-SAH (from 4 to 10 per 100.000 persons per year),<sup>44</sup> the absolute number is quite small. Statistical power seems to be sufficient for the comparison between patients and controls (primary aim), but the sample size limits our longitudinal prediction analyses, as we were not able to analyze interaction terms due to a limited number factors allowed in the final model (secondary aim). Furthermore, 81% of the study sample completed both follow-up measurements ( $n=42$ ). However, data of most patients could be analyzed by estimating the mean outcome using linear mixed model analyses. This modern statistical method takes into account the covariance between measurements within patients.<sup>45</sup>

In this observational study we have explored relationships between fatigue, fitness, activity, and sedentary behavior. In general, a major disadvantage of an observational design is that one should be careful when interpreting associations, as they do not

confirm causality.<sup>46</sup> For example, in this study we have made prediction models, and evaluated whether fitness was an independent predictor of fatigue. Such analysis may provide important clinical information about co-existence of problems; however, we do not know whether improvements in one variable would lead to reductions in the other. This needs to be confirmed in future intervention studies.

Some reflections are warranted regarding the VitaMove activity monitoring. The intended duration of measurement was three consecutive weekdays. Unfortunately, this was not uniformly achieved by all participants due to technological failures or user errors. It remains questionable whether short measurement periods are representative of general physical activity. Nevertheless, it has been reported that a 24-hour VitaMove measurement is adequate, to reliably determine activities and postures in daily living.<sup>47</sup> A major strength of the VitaMove activity monitor is that we could distinguish different types of activities (and sedentary behaviors) during the day, which provides detailed clinical information to help optimize and direct future rehabilitation programs.

## RECOMMENDATIONS FOR FUTURE RESEARCH

Improving levels of fitness, promoting physically active lifestyles and reducing sedentary behavior contribute to a healthy lifestyle in the general population,<sup>1, 8</sup> and may be even more important in a-SAH because these patients are highly fatigued, have considerably impaired physical fitness and are at risk of inactive and sedentary lifestyles. Findings from this thesis indicate that interventions are warranted and should involve both cardiorespiratory and strengthening exercise components. To evaluate changes in cardiorespiratory fitness in groups of patients with a-SAH, one may consider selecting the 6MWT as a clinical applicable alternative to progressive CPET.

Future studies should evaluate treatment paradigms to improve levels fitness in a-SAH, and study whether improved fitness levels reduces the severity of fatigue complaints. However, another important step is to evaluate whether there is an actual need for exercise training from a patients' perspective. In this patient group, psychological and cognitive problems, such as depressive symptoms, anxiety, mood disturbances and passive coping styles,<sup>24, 48</sup> are common and may interact with the compliance in exercise training.

Higher levels of daily physical activity (or exercise) improve levels of physical fitness.<sup>2</sup> Since patients with a-SAH have inactive lifestyles, that were associated with low fitness, active lifestyle interventions may be considered. However, previous studies showed that

it remains rather a challenge to elicit lasting lifestyle changes.<sup>49</sup> Therefore, an important step is to identify barriers and facilitators of physical activity in a-SAH. Next to inactive lifestyles, patients were highly sedentary with prolonged uninterrupted periods of sedentary behavior. Therefore, lifestyle interventions should not only focus on increasing physical activity, but should also focus on sedentary behavior which may provide additional health benefits in patients with a-SAH.

Since fatigue is a multifactorial construct, involving both psychological and biological factors,<sup>9</sup> we do not assume that exercise training is the 'golden bullet' treating fatigue. We rather suggest that higher fitness could provide a physical reserve to fatigue and therefore we think that exercise training is a potential contributor to a multimodal approach. Interventions targeting fatigue have not been studied in a-SAH. In patients with stroke, the combination of cognitive therapy and graded exercise training was found to be more effective in the treatment of persistent fatigue than standalone cognitive therapy.<sup>50</sup> This rehabilitation program included treadmill walking, strengthening exercise, and homework assignments (2h sessions, twice a week). Future interventions are warranted to investigate whether such rehabilitation programs can alleviate fatigue in patients with a-SAH as well.

## **CLINICAL IMPLICATIONS**

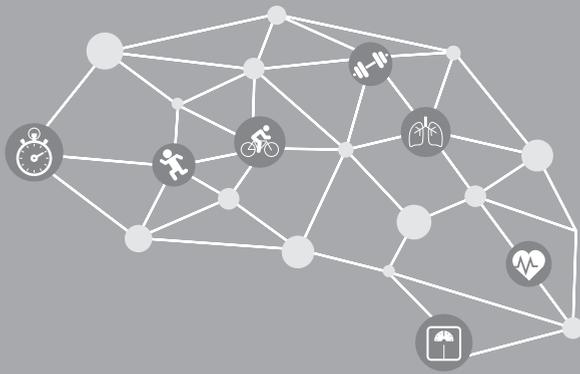
This is the first study on physical fitness, physical activity and sedentary behavior in patients with a-SAH and deserves attention in rehabilitation medicine. From a clinical perspective, health care professionals should be aware of the fact that patients with a-SAH may have poor fitness, inactive or sedentary lifestyles. According to the most recent Dutch guidelines for a-SAH,<sup>51</sup> a follow-up visit should be offered to the patient, and a multidisciplinary team should screen for cognitive dysfunction and emotional problems. However, until now there are no recommendations for activity or exercise. In our study we have made a first step towards a better understanding of the consequences of a-SAH on physical fitness, physical activity, sedentary behavior and associations with fatigue. Interventions are warranted to investigate the need and effectiveness of active lifestyle interventions (or exercise training) to improve fitness and optimize physical activity and sedentary behavior in patients with a-SAH. Further, multimodal rehabilitation programs seem necessary to treat persistent fatigue after a-SAH. Although we assume that all patients would benefit from such program, professionals should particularly be aware of those who have been treated with neurosurgical clipping.

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# Summary



The introductory **chapter 1** describes the clinical signs and symptoms of a subarachnoid hemorrhage (SAH), provides historical background, explains different treatment procedures, and gives a short background of the current knowledge of its consequences on daily life. Furthermore, this chapter explains the rationale of the present study. To better understand the long-term consequences of an aneurysmal subarachnoid hemorrhage (a-SAH), we have studied physical fitness, physical activity, sedentary behavior and fatigue in the first year after a-SAH. Insights in these measures may provide important clinical information, and could help to direct future interventions to improve the long-term outcomes in patients with a-SAH.

In **chapter 2** we describe the results of our study on physical activity (PA) and sedentary behavior (SB) in patients with a-SAH. PA and SB are objectively measured in free-living conditions by accelerometer based activity monitoring. Total activity and sedentary time are determined, and different types of activities distinguished. Intensity profiles are examined, and distribution metrics quantified. Activity profiles at six months are compared to that of sex- and age-matched controls. Patients are 25% less active, they tend to break activity time into shorter periods, and uninterrupted periods of sedentary time last longer compared to controls. Patients are highly sedentary and spend 8.5h in sedentary activities during the waking hours. Since PA and SB are both independent risk factors of poor cardiovascular health, future interventions should not only target PA, but should also focus on sedentary behavior.

The study described in **chapter 3** evaluates the isokinetic knee muscle strength in patients with a-SAH. Previous studies show that impaired muscle strength, especially in the lower-extremity, impacts the performance of physical activities and can trigger the onset of fatigue complaints. This chapter describes maximal voluntary isokinetic muscle strength of the knee extensors and flexors at six months. Muscle strength parameters are compared to that of sex- and age-matched controls. The results reveal that patients have considerably lower knee muscle strength than controls (21% to 36% lower). Further, the knee muscle strength is related to the severity of fatigue. In non-fatigued patients, the knee muscle strength is 11% to 32% lower compared to controls, whereas this is 28% to 47% in fatigued patients. Present findings are exploratory and indicate that interventions are necessary. Future research should consider strengthening exercise training in order to prevent debilitation conditions.

**Chapter 4** describes the cardiorespiratory fitness in patients with a-SAH. The criterion standard for cardiorespiratory fitness is peak oxygen consumption ( $\dot{V}O_{2peak}$ ) established during a progressive cardiopulmonary exercise test (CPET). In this study, the cardiorespiratory responses to a progressive CPET are obtained using indirect calorimetry. The

$\dot{V}O_{2peak}$  at six months is compared to that of sex- and age-matched controls. The  $\dot{V}O_{2peak}$  in persons with a-SAH is 31% lower compared to that in controls. Further,  $\dot{V}O_{2peak}$  seems to be lower in fatigued (37% lower than in matched controls) than in non-fatigued patients (26% lower than in matched controls).

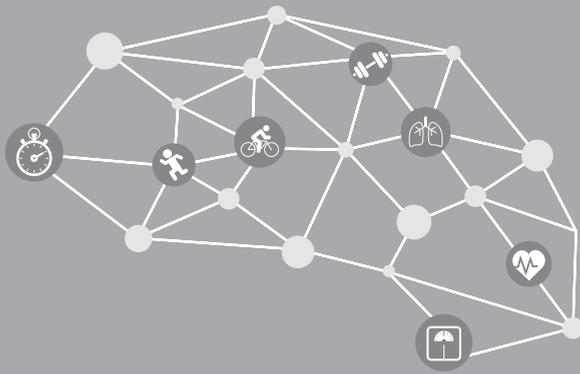
The  $VO_{2peak}$  obtained during CPET is the criterion standard for estimating the cardio-respiratory fitness. However, CPET with gas-exchange analyses requires specialized infrastructure with limited availability in most rehabilitation facilities. Further, the performance of CPET in a-SAH may be limited because of disease-related complaints. In **chapter 5** we describe a study in which we assessed whether we could predict  $\dot{V}O_{2peak}$  by performing a submaximal six-minute walk test (6MWT). The results show that the 6MWT can be selected to predict mean  $\dot{V}O_{2peak}$  in groups of patients with a-SAH, which may help to evaluate interventions in a clinical or research setting. However, the relatively large prediction error does not allow for an accurate prediction at an individual level.

Changes in fitness are evaluated over follow-up time, and relationships with activity, sedentary time and functional outcome explored. In addition, we assess whether fitness could be predicted by disease-related characteristics. The results of the study described in **chapter 6** reveals that levels of physical fitness remained low over the first year. Although small improvements are recognized (significant increment were found up to 6.2%), all fitness parameters remain significantly lower than reference values. Patients who are physically more active have higher levels of fitness, and patients with lower functional outcome (indicated by the Functional Independence Measure and Functional Assessment Measure) have lower knee muscle strength. Further, patients who had been treated with surgical clipping seem at risk of low fitness. These findings indicate that interventions are warranted and should involve both cardiorespiratory endurance and strengthening exercise components. Such program may also focus on the promotion of daily PA and should, in particular target patients with impaired functional outcome or those who had been treated with surgical clipping.

**Chapter 7** focusses on fatigue in a-SAH, and evaluates whether low fitness or inactive lifestyles play a role in the severity of fatigue complaints. In addition, we explore whether fatigue can be predicted by disease-related characteristics. Subjective measures of fatigue were evaluated at six and twelve months using the Fatigue-Severity-Scale (FSS). In our sample, fatigue was reported by approximately half of the patients, and its' severity did not diminish over follow-up time. The results indicate significant relationships between fitness and fatigue, in that patients with lower knee muscle strength are more severely fatigued. There is no evidence for relationships between activity or sedentary behavior and fatigue. Further, the severity of fatigue cannot be predicted by disease-

related characteristics. Interventions targeting fatigue seem necessary, and should consider incorporating exercise training as a potential contributor to improve fitness as this may provide a physical reserve to fatiguing conditions.

**Chapter 8** describes the main findings of this thesis and discusses the methodological considerations, both strengths and limitations. This chapter also addresses recommendations for future research and clinical implications.



# Samenvatting



Fysieke fitheid en lichamelijke activiteit hebben een gunstig effect op de gezondheid en kunnen een positief effect hebben op de lange-termijn uitkomsten van patiënten met chronische aandoeningen. Daarnaast zijn het belangrijke voorspellers voor mortaliteit en kunnen zij de kans op het krijgen van diabetes, obesitas en kanker verkleinen. Mensen die een subarachnoidale hersenbloeding (SAB) hebben overleefd klagen vaak over vermoeidheid. Vermoeidheidsklachten kunnen leiden tot het vermijden van lichamelijke activiteiten, wat vervolgens weer kan leiden tot een lagere fysieke fitheid. Aangezien fysieke fitheid en lichamelijke activiteit belangrijke voorspellers zijn voor de lange-termijn uitkomsten, is het van belang om hierover meer inzicht in te krijgen bij mensen met een SAB. Bevindingen uit dit onderzoek kunnen helpen om de gevolgen van een SAB beter te begrijpen en kunnen daarnaast bijdragen aan de ontwikkeling van revalidatieprogramma's. Het primaire doel van dit onderzoek is om de fysieke fitheid, fysieke activiteit en het sedentaire gedrag in het eerste jaar na een SAB in kaart te brengen. Daarnaast zijn er verbanden geëvalueerd tussen vermoeidheid, fysieke fitheid, fysieke activiteit en sedentair gedrag. Tevens is er onderzocht of vermoeidheidsklachten en een lage fysieke fitheid voorspeld kunnen worden aan de hand van patiënt karakteristieken.

**Hoofdstuk 1** geeft achtergrondgegevens van een SAB en tevens een kort overzicht van de huidige kennis betreffende behandeling en de lange termijn gevolgen. Dit hoofdstuk beschrijft de relevantie van het meten van beweeggedrag en fysieke fitheid bij mensen met een SAB en sluit af met de doelstellingen en een korte uiteenzetting van de inhoud van het proefschrift.

**Hoofdstuk 2** beschrijft de resultaten omtrent lichamelijke activiteit en sedentair gedrag bij mensen met een SAB. Lichamelijke activiteit is in het dagelijks leven objectief gemeten met behulp van het accelerometrie systeem: de VitaMove. Het totaal aan lichamelijke activiteit en sedentair gedrag is gemeten en verschillende activiteiten zijn gedifferentieerd (zoals lopen, fietsen en staan). Het beweeggedrag op zes maanden na SAB is vergeleken met dat van gezonde controlepersonen die een vergelijkbare leeftijd en hetzelfde geslacht hebben. Mensen na een SAB zijn 25% minder actief dan controlepersonen. Verder lijken mensen met een SAB hun fysieke activiteiten op te delen in kortere perioden, en duren de aaneengesloten perioden van sedentair gedrag langer dan bij controlepersonen. Ook vonden we dat mensen met een SAB 8.5 uur van de dag sedentair zijn. Aangezien lichamelijke inactiviteit en sedentair gedrag onafhankelijke risicofactoren zijn voor cardiovasculaire aandoeningen, zou een toekomstige interventie zich niet alleen moeten richten op het bevorderen van lichamelijke activiteit maar ook op het verminderen van sedentair gedrag.

**Hoofdstuk 3** beschrijft het onderzoek waarin de maximale isokinetische spierkracht van de knie extensoren en flexoren is onderzocht met behulp van een dynamometer. Om-

dat de maximale spierkracht een belangrijke rol speelt bij het uitvoeren van dagelijkse activiteiten en daarmee de ervaren vermoeidheid kan bepalen, zijn er relaties tussen de spierkracht en vermoeidheid onderzocht. De maximale spierkracht op zes maanden na SAB werd vergeleken met die van controlepersonen. Controlepersonen zijn individueel gematched op basis van geslacht en leeftijd ( $\pm 5$  jaar). De spierkracht van mensen met een SAB was 21% tot 36% lager in vergelijking met controlepersonen. Verder vonden we significante relaties tussen de maximale spierkracht en de ernst van de vermoeidheidsklachten. De spierkracht in de niet-vermoeide groep patiënten was 11% tot 32% lager dan in de controles, terwijl de spierkracht 28% tot 47% lager was in de groep vermoeide patiënten. Er werd geconcludeerd dat het wenselijk is om de spierkracht te vergroten. Daarnaast zijn er interventiestudies nodig om te onderzoeken of een toename in de spierkracht zorgt voor een afname in vermoeidheid.

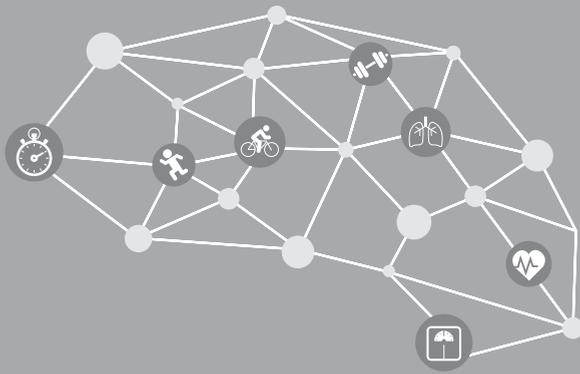
De gouden standaard voor het bepalen van de fysieke fitheid is de maximale zuurstofopname ( $VO_{2\text{piek}}$ ) en zegt iets over de cardiorespiratoire fitheid. In **hoofdstuk 4** wordt de  $VO_{2\text{piek}}$  van mensen met een SAB onderzocht. In dit hoofdstuk worden de resultaten van de maximale inspanningstest op een fietsergometer met daarbij ademgasanalyses gepresenteerd. De uitkomsten van de maximale inspanningstest zijn vergeleken met die van controlepersonen. De  $VO_{2\text{piek}}$  van mensen met een SAB was 31% lager dan bij de controlepersonen. Verder was de  $VO_{2\text{piek}}$  bij niet-vermoeide mensen met een SAB 26% lager dan bij de controlepersonen, terwijl dit 37% was voor vermoeide mensen met een SAB. Aangezien mensen met een SAB een lage fitheid hebben lijken interventies wenselijk om de fitheid te verhogen.

Hoewel de  $VO_{2\text{piek}}$  de gouden standaard is om de fysieke fitheid te bepalen, is het vaak lastig om maximale inspanningstesten met ademgasanalyses uit te voeren in een revalidatie setting. Daarnaast kunnen mensen met een SAB ook specifieke ziekte-gerelateerde klachten hebben waardoor het uitvoeren van een maximale inspanningstest niet haalbaar is. **Hoofdstuk 5** beschrijft het onderzoek waarin wordt geëvalueerd of een sub-maximale zes minuten wandeltest (6MWT) de  $VO_{2\text{piek}}$  kan voorspellen. Het regressiemodel toonde aan dat de zes minuten wandelafstand een sterke voorspeller is voor de  $VO_{2\text{piek}}$  dit veronderstelt dat de gemiddelde  $VO_{2\text{piek}}$  op groepsniveau voorspeld kan worden aan de hand van een sub-maximale 6MWT. Echter, deze bevinding ging gepaard met een forse afwijking van de schatting. Daarom is het niet mogelijk om de 6MWT af te nemen en op een individueel niveau een schatting te maken van de  $VO_{2\text{piek}}$ . Toekomstig onderzoek is nodig om een klinisch toepasbaar alternatief te vinden voor de maximale inspanningstest zodat deze kan worden gebruikt om nauwkeurige individuele schattingen te maken van de cardiorespiratoire fitheid van mensen met een SAB.

De veranderingen in de fysieke fitheid over de follow-up tijd, en relaties met lichamelijke activiteit, sedentair gedrag en functionele uitkomsten worden beschreven in **hoofdstuk 6**. Hoewel de cardiorespiratoire fitheid minimaal toenam over de follow-up tijd (significante toename tot 6.2%), bleven alle fitheidslevels significant lager dan de referentiewaarden. Verder blijkt uit ons onderzoek dat mensen met een SAB die lichamenlijk meer actief zijn een hogere fysieke fitheid hebben, terwijl een lagere functionele uitkomst is geassocieerd met een lagere spierkracht van de knie extensoren en flexoren. Daarnaast is er gevonden dat patiënten die een chirurgische clipping behandeling hebben ondergaan een lagere fysieke fitheid hebben dan mensen die een endovasculaire coiling behandeling hebben gehad. Omdat de fysieke fitheid in het eerste jaar na SAB laag is, lijken interventies nodig zijn om deze te verbeteren. Deze interventies zouden zich moeten richten op het verbeteren van zowel de cardiorespiratoire fitheid als de spierkracht. Daarnaast zouden interventies zich ook kunnen richten op het verhogen van dagelijkse lichamelijke activiteiten en zouden zich moeten richten op, maar niet beperken tot mensen met een lage functionele uitkomst of mensen die een clipping behandeling hebben ondergaan.

**Hoofdstuk 7** beschrijft de vermoeidheid in het eerste jaar na SAB. In dit hoofdstuk zijn ook relaties tussen vermoeidheid, lichamelijke activiteit, sedentair gedrag en fysieke fitheid onderzocht. Daarnaast hebben we geëvalueerd of de ernst van de vermoeidheidsklachten kan worden voorspeld aan de hand van patiënt-gerelateerde karakteristieken. Ongeveer de helft van de mensen met een SAB heeft last van vermoeidheidsklachten waarvan de ernst niet veranderde over de follow-up tijd. Er zijn significante relaties gevonden tussen de fysieke fitheid en vermoeidheid; patiënten die een lagere spierkracht hebben zijn ernstiger vermoeid. Er zijn geen relaties gevonden tussen lichamelijke activiteit of sedentair gedrag en vermoeidheid. Daarnaast bleek het niet mogelijk om vermoeidheid te voorspellen aan de hand van patiënt-gerelateerde karakteristieken. In dit hoofdstuk is geconcludeerd dat interventies nodig zijn om vermoeidheidsklachten te verminderen na een SAB omdat deze niet minder worden gedurende het eerste jaar. Aangezien vermoeidheid een multifactorieel probleem is, denken wij niet dat een eenzijdige fysieke training de vermoeidheidsklachten zal verminderen, we denken wel dat het een potentiële bijdrage kan leveren aan een multimodale behandeling van vermoeidheid na SAB.

**Hoofdstuk 8** bevat de algemene discussie van dit proefschrift. Dit hoofdstuk beschrijft de belangrijkste bevindingen en de interpretatie van de resultaten. In dit hoofdstuk beschrijven we ook sterke en zwakke punten van het onderzoek, doen we aanbevelingen voor toekomstig onderzoek en geven we klinische implicaties.



# Dankwoord



Nog een paar laatste woorden en dan weet ik dat dit avontuur er op zit. Met de finishlijn in zicht wil ik in dit onderdeel van het proefschrift iedereen bedanken die op enigerlei wijze betrokken is geweest bij de totstandkoming ervan. Een aantal mensen wil ik in het bijzonder bedanken.

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Een zeer belangrijke rol in dit promotietraject is vervuld door mijn eerste copromotor dr. van den Berg-Emons. Beste Rita, zonder jouw begeleiding had ik dit traject niet succesvol kunnen doorlopen. Ik ben je zeer erkentelijk voor jouw betrokkenheid, wetenschappelijke deskundigheid en positieve instelling. Onze gesprekken heb ik altijd als erg prettig ervaren. Ik heb bijzonder veel van je geleerd.

Dr. van Kooten, beste Fop, als tweede copromotor werd jouw rol groter naarmate het traject vorderde. Dank voor je positieve en motiverende feedback en de tijd die je in mij hebt geïnvesteerd.

Many thanks to the members of my thesis committee for their effort to read and judge my thesis.

Mijn grootste dank gaat uit naar de deelnemers aan dit onderzoek. Bedankt voor het uitvoeren van de zware inspanningstesten, het invullen van de vragenlijsten en het dragen van de activiteitenmonitors. Zonder jullie deelname was dit boekje er niet geweest.

Verder ben ik de medewerkers van het klinisch beweeglaboratorium die hebben bijgedragen aan de uitvoering van de metingen zeer erkentelijk. Een extra woord van dank gaat uit naar Emiel Sneekes, die naast de projectcoördinatie ook kritisch mijn artikelen heeft becommentarieerd.

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Mijn beide paranimfen Nienke en Kerstin wil ik bedanken dat zij naast mij willen staan op deze bijzondere dag. Ik vind het heel leuk om te zien dat onze trajecten zo gelijk opgaan. Nienke, gedurende het gehele traject ben jij mijn directe sparringpartner geweest, bedankt voor alle steun in de afgelopen jaren. Kerstin, fijn dat je ook op deze dag naast mij wilt staan.

Mijn vaste werkplek was op de 16e etage van het Erasmus MC. Collega's van de 16e, ik wil jullie allen bedanken voor de goede sfeer, gezellige borrels en uitstapjes. Jullie hebben er voor gezorgd dat ik altijd met veel plezier naar het werk ging.

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Veel dank gaat uit naar de collega's van de afdeling Revalidatiegeneeskunde van het Erasmus MC. Bedankt voor de inspirerende refereerbijeenkomsten en interesse in mijn onderzoek. In het bijzonder wil ik prof.dr. Henk Stam bedanken, die als afdelingshoofd voor een veilige werkomgeving heeft gezorgd waardoor ik mijn onderzoeksvaardigheden optimaal heb kunnen ontwikkelen.

Lianne Peppel, wij hadden beiden de ambitie om naast een promotietraject ook de opleiding Epidemiologie te doen. De combinatie van essays schrijven voor de opleiding en het promotietraject gaande houden was niet altijd even eenvoudig. Ik wil je bedanken voor je nuchtere blik en vrolijke inbreng.

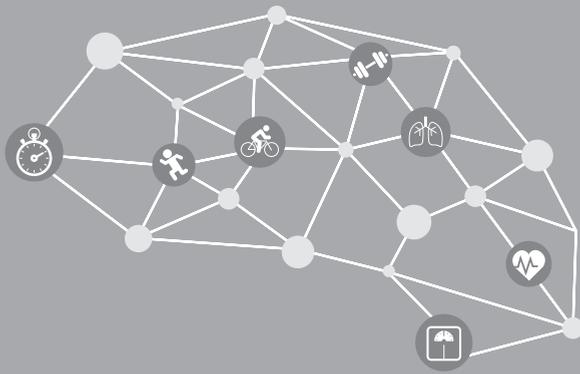
Dear colleagues of the NIHES graduation class 2016, I learnt from our interesting discussions we had during our NIHES-meetings, excellent contributions in class, cultural traditions, languages and all other things. Thanks for being part of this all.

Mijn huidige collega's van het Kennisinstituut van de Federatie Medisch Specialisten, oud-collega's van Rijndam Arbeidsrevalidatie en het Erasmus MC-Sophia wil ik bedanken voor de vele memorabele momenten, goede gesprekken, mentale ondersteuning en belangstelling in mijn onderzoek.

Mijn familie en vrienden wil ik bedanken voor de interesse maar vooral voor de nodige ontspanning en gezelligheid die het mogelijk maakten om dit proefschrift te kunnen

maken. Mijn tweelingzus Lianne bedank ik voor haar mentale support tijdens het schrijven. In het bijzonder wil ik hier mijn ouders noemen. Lieve mam en pap, bedankt voor de onvoorwaardelijke steun en liefde. De vanzelfsprekendheid waarmee jullie met mij meeleven met belangrijke en minder belangrijke dingen is gewoonweg top! Ik ben blij dat jullie er zijn.

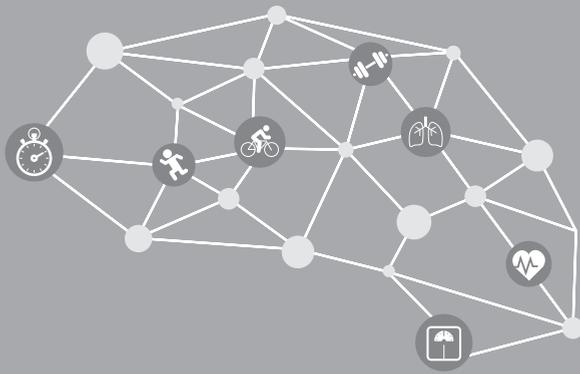
Tenslotte een woord voor Kerstin. Kerstin, de afgelopen periode hebben wij hard gewerkt aan de afronding van onze beide proefschriften. Doordat we samen optrokken leek het soms wel vanzelf te gaan. Ik kijk uit naar de avonturen die voor ons liggen. Je bent precies alles wat ik nodig heb.



## About the author



Wouter Harmsen was born in Schiedam on the 14th of August 1987. He attended secondary school at Spieringshoek (VWO) in Schiedam, where he graduated in 2006. In the same year he started his study Human Movement Sciences at the VU University in Amsterdam. In 2010 he obtained his Bachelor's degree, with a specialization in rehabilitation. During his master's he did an internship at Reade Rehabilitation in Amsterdam and finished his master's in 2011. Before he started to work on the research described in this thesis, he worked at the pediatric inpatient rehabilitation clinic of Rijndam Rehabilitation and the department of Rehabilitation Medicine of the Erasmus MC University Medical Center in Rotterdam. In 2014 he started his PhD on the long-term consequences of a-SAH at the department of Rotterdam Neurorehabilitation Research of Rijndam Rehabilitation in Rotterdam. In the same year he started with a Master of Science in Epidemiology at the Netherlands Institute of Health Sciences (NIHES) and obtained his Master's degree in health sciences in 2016. During his PhD he also worked at the Sophia Children's Hospital and performed research on the long-term health consequences of invasive neonatal surgery. He also worked for the outpatient 'return-to-work' clinic of Rijndam Rehabilitation in Rotterdam. Currently, he works at the Knowledge Institute of the Dutch Association of Medical Specialists and contributes to the development of evidence based medical guidelines.



## List of publications



**Harmsen WJ**, Ribbers GM, Heijnenbrok-Kal MH, Khajeh L, Sneekes EM, van Kooten F, Neggers SJ, van den Berg-Emons RJ. Fatigue after aneurysmal subarachnoid hemorrhage is highly prevalent and related to low physical fitness: a one year follow-up study. *Submitted*

**Harmsen WJ**, Khajeh L, Ribbers GM, Sneekes EM, van Kooten F, Neggers SJ, Heijnenbrok-Kal MH, van den Berg-Emons RJ. Physical fitness remains low over the first year after aneurysmal subarachnoid hemorrhage, relates to physical inactivity and functional outcome, and is predicted by surgical clipping. *Submitted*

**Harmsen WJ**, Ribbers GM, Heijnenbrok-Kal MH, Bussmann JB, Sneekes EM, Khajeh L, van Kooten F, Neggers SJ, van den Berg-Emons RJ. Inactive lifestyles and sedentary behavior in persons with chronic aneurysmal subarachnoid hemorrhage: evidence from accelerometer-based activity monitoring. *Journal of NeuroEngineering and Rehabilitation*. 2017 Nov 23;14(1):120

**Harmsen WJ**, Ribbers GM, Slaman J, Heijnenbrok-Kal MH, Khajeh L, van Kooten F, Neggers SJ, van den Berg-Emons RJ. The six-minute walk test predicts cardiorespiratory fitness in individuals with aneurysmal subarachnoid hemorrhage. *Top Stroke Rehabil*. 2017 May;24(4):250-255.

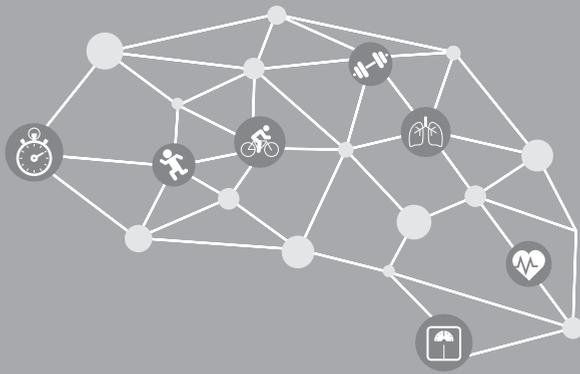
**Harmsen WJ**, Ribbers GM, Zegers B, Sneekes EM, Praet SF, Heijnenbrok-Kal MH, Khajeh L, van Kooten F, Neggers SJ, van den Berg-Emons RJ. Impaired muscle strength may contribute to fatigue in patients with aneurysmal subarachnoid hemorrhage. *Int J Rehabil Res*. 2017 Mar;40(1):29-36.

**Harmsen WJ**, Aarsen FJ, van der Cammen-van Zijp MHM, van Rosmalen JM, Wijnen RMH, Tibboel D, IJsselstijn H. Developmental problems in patients with oesophageal atresia: a longitudinal follow-up study. *Arch Dis Child Fetal Neonatal Ed*. 2017 May;102(3):F214-F219.

**Harmsen WJ**, Ribbers GM, Zegers B, Sneekes EM, Heijnenbrok-Kal MH, Khajeh L, van Kooten F, Neggers SJ, van den Berg-Emons RJ. Impaired cardiorespiratory fitness after aneurysmal subarachnoid hemorrhage. *J Rehabil Med*. 2016 Oct 12;48(9):769-775.

**Harmsen WJ**, Bussmann JB, Selles RW, Hurkmans HL, Ribbers GM. A Mirror Therapy-Based Action Observation Protocol to Improve Motor Learning After Stroke. *Neurorehabil Neural Repair*. 2015 Jul;29(6):509-16.

Toussaint-Duyster LCC, van der Cammen-van Zijp MHM, Takken T, **Harmsen WJ**, Tibboel D, van Heijst AFJ, de Blaauw I, Wijnen RMH, van Rosmalen J, IJsselstijn H. Improving exercise capacity following neonatal respiratory failure; a randomized controlled trial. *Submitted*



# PhD Portfolio



## SUMMARY OF PhD TRAINING AND TEACHING

<b>Name PhD Student:</b>	Wouter J. Harmsen	<b>PhD period:</b>	2014-2017
<b>Erasmus MC Department:</b>	Rehabilitation Medicine	<b>Promotor:</b>	Prof.dr. G.M. Ribbers
<b>Research School:</b>	Health Sciences (NIHES)	<b>Supervisors:</b>	Dr. F. van Kooten Dr. H.J.G. van den Berg-Emons

### 1. PhD Training

	Year	Workload (hours/ECTS)
<b>General academic courses</b>		
- Endnote (medical library)	2013	3 hours
- Literature search	2013	3 hours
- BROK course	2013	35 hours
- Science integrity	2014	0.3 ECTS
- English biomedical writing and communication	2015	4.0 ECTS
<b>Research Skills</b>		
MSc in Health sciences, specialisation: 'Epidemiology' (NIHES)		
<i>Health sciences</i>		
- Study design	2015	4.3ECTS
- Biostatistical methods: basic principles	2015	5.7 ECTS
- Biostatistical methods: advanced statistics	2015	4.3 ECTS
- English language	2015	1.4 ECTS
- Introduction to Medical writing	2015	2.0 ECTS
- Oral research presentation	2015	1.4 ECTS
- Research period PIN Health sciences	2015	28.7 ECTS
<i>Epidemiology</i>		
- Methodologic topics in Epidemiologic research	2015	1.4 ECTS
- Principles of research in medicine and epidemiology	2015	0.7 ECTS
- Methods of public health research	2015	0.7 ECTS
- Introduction to public health	2016	0.7 ECTS
- Primary and secondary prevention research	2016	0.7 ECTS
- Social epidemiology	2016	0.7 ECTS
- Fundamentals of medical decision making	2016	0.7 ECTS
<i>Elective courses</i>		
- Methods of clinical research	2016	0.7 ECTS
- Topics in Meta-analysis	2016	0.7 ECTS
- Health Economics	2016	0.7 ECTS
- Methods of Health services research	2016	0.7 ECTS

- History of epidemiologic ideas	2016	0.7 ECTS
- The practice of epidemiologic analysis	2016	0.7 ECTS
- Advanced topics in medical decision making	2016	0.7 ECTS
- Nutrition and physical activity	2016	1.4 ECTS
- Public health research	2016	5.7 ECTS
- From problem to solution in public health	2016	1.1 ECTS

### In depth courses

- Basic life support adults	2014	4 hours
- Basic life support children	2014	4 hours
- ECG interpretation	2014	8 hours
- Open Clinica – Electronic data capture for clinical research	2015	24 hours
- Introduction to career planning for PhD's, Erasmus MC, Rotterdam	2016	8 hours

### Presentations

- Oral presentation: Physical fitness after a-SAH: a cross-sectional study, regionaal refereer, Rijndam Rehabilitation Center, Rotterdam	2014	15 hours
- Oral presentation: A mirror therapy-based action observation protocol to improve motor learning after stroke, DCRM, Egmond aan Zee	2014	15 hours
- Poster Presentation: Impaired cardiopulmonary fitness after a-SAH: cross-sectional results, ACRM, Toronto	2014	10 hours
- Poster Presentation: A mirror therapy-based action observation protocol to improve motor learning after stroke, ACRM, Toronto	2014	10 hours
- Poster Presentation: A mirror therapy-based action observation protocol to improve motor learning after stroke, NNR, Maastricht	2015	10 hours
- Poster Presentation: Motor performance and exercise capacity in children with esophageal atresia, EA-conference, Rotterdam	2015	10 hours
- Oral presentation: Physical fitness and physical behavior after a-SAH, Hersenletselcongres, Ede	2016	15 hours
- Oral presentation: Objective measurement of physical behavior after a-SAH, Conference of Human Movement Sciences, Maastricht	2016	15 hours
- Oral presentation: Physical fitness and physical behavior after a-SAH, Neurorehabilitation Neural Repair, Maastricht	2017	10 hours
- Oral presentation: Physical deconditioning and fatigue in a-SAH, International Brain Injury Association (IBIA), New Orleans	2017	15 hours
- Oral presentation: Oral presentation: Physical fitness and physical behavior after a-SAH: a one-year follow-up, Dutch Conference of Rehabilitation Medicine, Maastricht	2017	10 hours

### International conferences

- SMALLL-conference Society for Movement Analysis Laboratories	2013	8 hours
- Dutch Conference of Rehabilitation Medicine, Egmond aan Zee	2013	8 hours
- American Conference of Rehabilitation Medicine, Toronto	2014	32 hours
- Dutch Conference of Rehabilitation Medicine, Rotterdam	2014	16 hours

- Neurorehabilitation Neural Repair, Maastricht	2015	16 hours
- Methods and research: physical activity and nutrition, Cambridge	2016	24 hours
- Conference of Human Movement Sciences, Maastricht	2016	8 hours
- International Brain Injury Association, New Orleans	2017	16 hours
- Neurorehabilitation and Neural Repair, Maastricht	2017	8 hours
- Dutch Conference of Rehabilitation Medicine, Maastricht	2017	8 hours

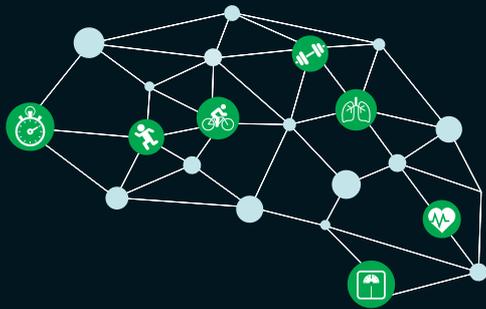
### Other

- Participating in research meetings dept. of Rehabilitation medicine, Erasmus MC, Rotterdam	2013-2016	150 hours
- Participating research meetings dept. of Rotterdam Neurorehabilitation Research (RoNeRes), Rotterdam	2014-2016	40 hours
- Organizing research meetings dept. of rehabilitation medicine, Erasmus MC, Rotterdam	2014-2015	40 hours
- Annual research poster dept. Rehabilitation medicine, Erasmus MC, Rotterdam	2015	10 hours
- Research Integrity meetings dept. of Rehabilitation medicine, Erasmus MC, Rotterdam	2015-2016	16 hours
- Co-editor 'Medigrip' application for rehabilitation specialists	2014-2016	40 hours

## 2. Teaching

### Lecturing

- Research skills (minor Rehabilitation Medicine, Rehabilitation medicine, Erasmus MC, Rotterdam)	2015	24 hours
- Physical activity and Sedentary behaviour: norm-values (minor Rehabilitation medicine, Rehabilitation medicine, Erasmus MC, Rotterdam)	2015	24 hours



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