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FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
*master in de revalidatiewetenschappen en de
kinesitherapie*

Masterproef

Significant deterioration of cardiopulmonary exercise tolerance after minimally
invasive aortic valve replacement

Promotor :
Prof. dr. Dominique HANSEN

Eline Briels , Maartje Vanderlinden

*Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen
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Acknowledgement

Before introducing this master thesis, we would like to express our gratitude to some people who were of great support during the development of this master thesis. First, we would like to thank all the participants who volunteered to participate in our study. Special thanks goes to the patients undergoing minimally invasive aortic valve replacement at Jessa Hospital, Hasselt, who engaged themselves to perform different exercise tests in their pre- and postoperative conditions. Also special thanks to our family members, acquaintances and volunteers who offered their time to serve as our healthy controls. Second, we would like to thank our promotor, Prof. Hansen, for his guidance during the assessment, analyze and writing process and Hajar Boujemaa, student Master of Biomedical Sciences at Hasselt University, who contributed to this study by testing the patients undergoing minimally invasive aortic valve replacement.

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Research context

This study is situated within the research domain of rehabilitation of internal disorders and is an important requirement for the acquisition of a Master in Rehabilitation Science and Physical Therapy at Hasselt University.

Minimally invasive aortic valve replacement is a recently developed surgical technique which is used more and more frequently in the treatment of aortic valve stenosis instead of the conventional technique, which is much more invasive¹. This procedure leads to better clinical postoperative outcomes, however functional outcomes after minimally invasive aortic valve replacement remain uninvestigated^{2,3}.

This master thesis investigated the short term cardiopulmonary and muscular oxidative outcomes after minimally invasive aortic valve replacement through hemi-sternotomy. This study was part of a larger study which will investigate these outcomes in the long term. Based on these short and long term outcomes, an exercise program will be developed in the future. Finally, this exercise program will be investigated for its appropriateness in this patient population. However, these latter two research questions fall beyond the scope of this master thesis.

For this study a new study protocol, drafted by Prof. Hansen and colleagues, was used. Based on our feedback, some additions and adjustments were made to this study protocol. Recruitment and data acquisition of the control group were performed by both students. Exercise testing of these healthy controls was executed by both students under supervision of our promotor. Recruitment and data acquisition of the patient group were performed by Hajar Boujema, a master's student Biomedical Sciences at Hasselt University. Finally the data analysis and the writing process were performed by both students.

¹ Bonow, R. O., et al. (2008). "Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons." J Am Coll Cardiol **52**(13):e1-142.

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Stahli, B. E., et al. (2012). "Assessment of inflammatory response to transfemoral transcatheter aortic valve implantation compared to transapical and surgical procedures: a pilot study." J Invasive Cardiol **24**(8):407-411.

³ Myles, P. S. (2014). "Meaningful outcome measures in cardiac surgery." J Extra Corpor Technol **46**(1):23-7.

1. ABSTRACT

Background: The recently developed minimally invasive aortic valve replacement (mAVR) technique for the treatment of aortic valve stenosis (AS) is known to lead to better clinical outcomes, e.g. lower inflammatory response and infection rate. However the influence on cardiopulmonary and muscular oxidative function remains unclear.

Objectives: To describe the impact of mAVR on cardiopulmonary and muscular oxidative function during exercise early after surgery and to explore pre- and perioperative factors related to anomalous recovery of these functions during exercise testing.

Participants: Sixteen patients with severe aortic stenosis (AS) undergoing mAVR at Jessa Hospital, Hasselt (7 males; mean±SD 68.2±12.3 years) were included. They were evaluated preoperatively and at five days and three weeks postoperative. Thirty matched healthy controls (21 males; mean±SD 69.6±5.1 years) served as preoperative reference subjects.

Measurements: Primary outcome measures were submaximal cardiopulmonary exercise test (CPET) parameters: oxygen uptake ($\dot{V}O_2$), minute ventilation (V_e), resting heart rate (HR), heart rate percentage (%HR), tidal volume (V_t), oxygen pulse (O_2 pulse), respiratory exchange ratio (RER), respiratory equivalent for oxygen (EqO_2) and carbon dioxide ($EqCO_2$), mean response time (MRT), blood lactate and rate of perceived exertion (RPE). Secondary outcome measures were patient characteristics and peri-operative data.

Results: Compared to healthy controls, a higher MRT, EqO_2 , $EqCO_2$ and lower O_2 pulse was observed during exercise in AS patients ($p < 0.05$). Furthermore, within mAVR patients, deterioration of $EqCO_2$, EqO_2 , V_e and RPE was observed five days and/or three weeks after surgery ($p < 0.05$). Gender, body mass index, perioperative mechanical ventilation time and preoperative RER, V_e and V_t were positively correlated with postoperative deterioration of cardiopulmonary function during exercise, whereas a negative correlation was observed for preoperative $EqCO_2$ and O_2 pulse.

Conclusion: Cardiopulmonary exercise tolerance was significantly lowered in patients with severe aortic stenosis and further deteriorated early after mAVR. Therefore, rehabilitation should emphasize on cardiopulmonary exercise programs.

2. INTRODUCTION

Aortic stenosis (AS) is a chronic, progressive valve disease and the most frequent acquired heart valve disease in Europe (Lung et al., 2003). According to the ACC/AHA guidelines, the degree of AS is usually determined by the aortic valve area: a valve area $> 1.5 \text{ cm}^2$ is considered mild, a valve area of 1.0 to 1.5 cm^2 is considered moderate and a valve area $\leq 1.0 \text{ cm}^2$ is considered severe AS (Bonow et al., 2008). Patients usually remain asymptomatic in mild AS (Rosenhek et al., 2000), while more severe AS is accompanied by various indirect (e.g. increased left ventricular myocardial mass) and direct symptoms (e.g. chest pain, shortness of breath, syncope and sudden cardiac death) (Vahanian et al., 2012).

Symptomatic AS patients require surgical intervention: patients suffering from severe AS are prone to premature death when left untreated (Vahanian et al., 2012). Aortic valve replacement leads to reductions in morbidity and mortality, and elevations in quality of life (Brown et al., 2008; Shan L, Saxena, McMahon, Wilson, & Newcomb, 2013). Conventional aortic valve replacement (cAVR) is performed via full sternotomy and by use of cardiopulmonary bypass (Schmitto, Mohr, & Cohn, 2011), and is performed approximately 275.000 times per year worldwide (Rabkin & Schoen, 2002). However, minimally invasive replacement of the aortic valve (mAVR) is more often executed during the last decade, in which for example hemi-sternotomy is executed (Bonow et al., 2008). This procedure leads to smaller inflammatory responses, less pain and blood loss, lower infection risk, a better cosmetic result, lower costs and shorter intubation time and hospital stay (Adrie et al., 2015; Erdoes et al., 2015; Falcone et al., 2013; Goetzenich et al., 2011; Higgins et al., 2011; Lindman et al., 2014; O'Brien et al., 2011; Stahli et al., 2012; Phan, Xie, Di Eusano, & Yan, 2014; Lim et al., 2014). Due to these clinical advantages, and despite the required skill and required learning curve of the cardiothoracic surgeon, it is anticipated that mAVR will be executed more frequently.

Many efforts are made to improve patient outcome after mAVR, but most studies focus on hard endpoints only, i.e. adverse events and mortality, in this endeavor. However, 'softer' and more functional outcome parameters should be considered more often during follow-up after cardiothoracic surgery (Myles, 2014), as this makes earlier intervention possible in case of complicated recovery, sometimes even before onset of symptoms.

Exercise testing may be highly relevant in this attempt. For example, some exercise parameters predict worse outcome in patients in need of aortic valve replacement, if left untreated (Alborino, Hoffmann, Fournet, & Bloch, 2002; Amato, Moffa, Werner, & Ramires, 2001; Das, Rimington, & Chambers, 2005; Lancelotti et al., 2005). Additionally, a lower peak oxygen uptake and oxygen pulse (indirect indicator of cardiac stroke volume) during exercise are independently related to greater mortality risk in patients with severe aortic stenosis (Dhoble et al., 2014). These are examples of softer endpoints with significant prognostic value.

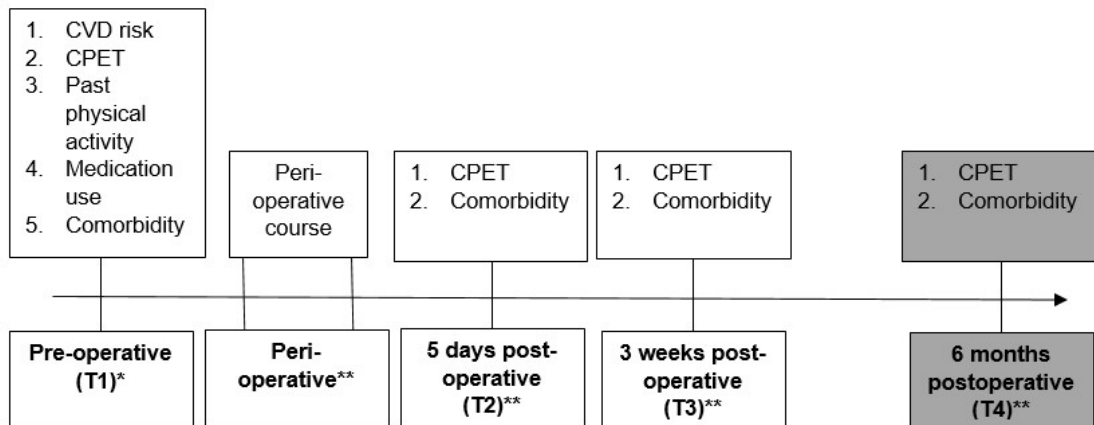
Next to the examination of exercise tolerance, cardiopulmonary exercise testing may also have great potential to examine detailed changes in cardiac and pulmonary function, but also in muscular oxidative function, after mAVR. Such systematic follow-up of patients after mAVR, including examination ahead of surgery, may lead to a greater understanding of how postoperative recovery is manifested, whether additional interventions should be implemented to improve this recovery and whether certain changes in cardiopulmonary and muscular function during exercise after surgery are related to worse outcomes. In addition, preoperative cardiopulmonary exercise tests may even be of use to estimate peri- and postoperative outcomes. Even though changes in physical fitness have been assessed during rehabilitation programs in patients with mAVR (Russo et al., 2014; Völler et al., 2015), such detailed analysis of changes in cardiopulmonary and muscular function during exercise (early) after mAVR is absent.

The aim of this study is therefore 1. To describe changes in cardiopulmonary and muscular oxidative function during exercise early after mAVR and 2. To explore pre- and perioperative factors related to anomalous recovery in cardiopulmonary and muscular function during exercise testing after mAVR. It was hypothesized that 1. Significant improvements in cardiac, but not muscular or ventilatory, function during exercise can be observed after mAVR. In such case, early muscular and/or pulmonary rehabilitation intervention may be indicated to facilitate recovery, and 2. Certain pre- and perioperative factors are related to complicated recovery in cardiopulmonary and muscular function during exercise after mAVR. In such case, cardiothoracic surgeons may need to adapt surgical techniques to facilitate recovery or initiate preoperative interventions to deal with reversible risk factors.

3. METHODS

3.1 Study design

The study consisted of a cross-sectional part and a prospective observational part. First, in the cross-sectional part, preoperative data from the submaximal cardiopulmonary exercise test were compared between AS patients (n=16) and healthy controls (n=30) to achieve a reference standard for the mAVR patients. Second, the observational part was executed, in which all measurements were performed at three time points in patients with AS undergoing mAVR. The entire study design of the cross-sectional and prospective observational part with time points and measurements are mentioned in figure 1. Our master thesis part 2 investigated the short-term effects up to the first three postoperative weeks (T3) and was part of a larger study, which will further investigate the long-term effects up to six months (T4). Finally, correlations between pre- and perioperative parameters and postoperative changes in exercise parameters were investigated.



**, control group and mAVR group; **, mAVR group only; CVD, cardiovascular disease; CPET, cardiopulmonary exercise test*

Figure 1 Study time points and measurements of the cross-sectional and prospective observational study

3.2 Participants

3.2.1 Selection criteria

Patients undergoing mAVR at Jessa Hospital, Hasselt between December 2016 and March 2017, were included in this study if they fulfilled the following criteria: Dutch speaking, Caucasian and having severe AS (valve area ≤ 1.0 cm²). Healthy controls were included if they were Dutch speaking, Caucasian, apparently healthy and matched for age, gender and BMI.

Patients were excluded in case of following conditions: coronary artery disease, peripheral arterial disease, not being able to execute an exercise test and combined surgery (e.g. mAVR + coronary artery bypass grafting (CABG)). Healthy controls were excluded if they had any chronic disease or exercise limiting condition.

3.2.2 Recruitment

Because such study has not been executed before, not even after conventional aortic valve replacement, it was not possible to execute an a priori sample size calculation. Arbitrary, it was decided to complete follow-up of 30 patients undergoing mAVR in Jessa Hospital, Hasselt. Taking a drop-out of 20% during follow-up into account, a target of 36 subjects was pursued. However, this target was difficult to reach due to the scarce available population undergoing this surgical technique at Jessa Hospital. The finally achieved target was submitted to an interim statistical power analysis to determine the observed statistical power. Patients undergoing mAVR were recruited at Jessa Hospital, Hasselt. The surgeon invited patients fulfilling the inclusion criteria during the consultation to participate in this study. A same number of healthy controls, i.e. 36, was recruited by personal invitation in different communities, public places, acquaintances of the researchers, etc. As the control group was tested before the patient group due to practical reasons, healthy controls could not be prospectively matched by the characteristics of the patients who were included later in this study. Consequently, matching of the healthy controls was performed by analyzing the characteristics of patients undergoing mAVR at the Jessa Hospital, Hasselt in 2014-2016.

3.2.3 Medical ethics

The study protocol was approved by a medical ethical committee (B243201629467, October 10th 2016) and informed consents were obtained from all subjects.

3.3 Study procedure

3.3.1 Intervention

AS patients underwent mAVR at Jessa Hospital, Hasselt. The procedure was performed through a hemi-sternotomy with an incision of four to five centimeters and was performed under general anesthesia. During the procedure a cardiopulmonary bypass was used. Mean length of stay at the Intensive Care Unit (ICU) was 35 hours and mean hospitalization duration was six days. Pictures of this surgical intervention are added in appendix 1 (Jessa Hospital, Cardiac Surgery, 2015). The healthy controls did not undergo any intervention.

3.3.2 Outcome measures

3.3.2.1 Primary outcome measures

Cardiopulmonary exercise test (CPET)

To obtain detailed information of cardiac, pulmonary and muscular function during exercise, CPET was executed. Subjects performed a submaximal cardiopulmonary exercise test with constant work load on an electronically braked cycle ergometer (eBike Basic, General Electric GmbH, Bitz, Germany). Subjects were seated on bike for three minutes to obtain resting data. Next, subjects were instructed to cycle at a rate of 70 rounds per minute (rpm), against a resistance corresponding to 25% of predicted maximal cycling power output (W_{max}), for six minutes (Spencer, Murias, Lamb, Kowalchuk, & Paterson, 2011). After six minutes of cycling subjects remained seated on the bike for an additional six minutes, after which a second and third six minutes exercise bout were initiated, each time interspersed by a six-minutes recovery. Predicted W_{max} was based on gender, age, body weight and height, and calculated by previously published formulae (Jones, Makrides, Hitchcock, Chypchar, & McCartney, 1985).

Subjects were advised not to perform any exercise the day before or at the day of testing, and only eat a light meal at least two hours prior to testing. Pulmonary gas exchange was continuously measured breath-by-breath with a mass spectrometer and volume turbine system (Jaeger Oxycon, Erich Jaeger GmbH, Germany). During the exercise test, oxygen uptake (VO_2 , ml/min) and minute ventilation (V_e , l/min) were assessed breath-by-breath, after which these data were averaged every ten seconds. Heart rate was continuously monitored by 12-lead ECG device. Predicted maximal heart rate was calculated by $220 - \text{age}$.

Following each exercise bout, capillary blood samples were obtained from the fingertip to analyze blood lactate concentrations (mmol/l), using portable lactate analyzer (Accutrend plus©, Roch Diagnostics Limited, Sussex, UK). This portable analyzer has been shown to have excellent correlations with reference lactate analyzers (Baldari, Bonavolonta, &Emerenziani, et al., 2009). At the end of each exercise bout ratings of perceived exertion (RPE) were scored by the subjects on a 6-20 Borg scale.

By the averaging of cardiac (oxygen pulse (VO_2/HR), resting HR, HR percentage), pulmonary (O_2 uptake equivalent (VE/VO_2 , reflecting O_2 uptake efficiency), CO_2 elimination equivalent (VE/VCO_2 , reflection CO_2 elimination efficiency), minute ventilation (VE), tidal volume (Vt), respiratory exchange ratio (RER)) and muscular (blood lactate) parameters at the end of each exercise bout (final minute), a detailed analysis of function of these systems was possible.

From this test, exercise-onset VO_2 kinetics were calculated algebraically and expressed as mean response time (MRT) (Arena, Humphrey, Peberdy, &Madigan, 2003). The outcome parameter that was derived from this method correlates well with, and is not significantly different from, the time constant (Arena, Humphrey, Peberdy, &Madigan, 2003). Resting VO_2 was calculated as the VO_2 during the final minute before exercise. Steady-state VO_2 was defined as the averaged value between the fifth and sixth minute of cycling. The difference between the rest VO_2 and steady-state VO_2 , multiplied by exercise time (six minutes), was defined as the expected amount of VO_2 during the entire exercise bout. However, in order to examine skeletal muscle oxidative capacity by calculating exercise-onset VO_2 kinetics, it was important to ignore the cardiodynamic phase of kinetics. As a result, the first 20 seconds of data after onset of exercise were eliminated (Jones, Wilkerson, Koppo, Wilmshurst, &Campbell, 2003). The sum of VO_2 above resting level was defined as the actually achieved VO_2 during the entire exercise bout. The oxygen deficit was then calculated by: expected amount of VO_2 – actually achieved VO_2 . Division of this oxygen deficit by the difference between rest VO_2 and steady-state VO_2 equals MRT. The resultant MRT, multiplied by 60, finally produces a value expressed in seconds, and this outcome was used throughout this manuscript to quantify exercise-onset VO_2 kinetics. Finally, the three MRT's that were obtained from the three exercise bouts were averaged.

Experimental evidence clearly indicates that exercise-onset VO_2 kinetics are significantly correlated with maximal VO_2 ($r=-0.80$, $p<0.05$) (Powers, Dodd, & Beadle, 1998), and that exercise-onset VO_2 kinetics are faster in skeletal muscle with predominantly slow-twitch fibers, and/or with increased activation of oxidative muscle enzymes (Barstow, Jones, Nguyen, & Casaburi, 1996; Hughson, 2009). Interestingly, exercise-onset VO_2 kinetics are significantly slowed in subjects with chronic diseases that are typically characterized by a lower exercise capacity, such as lung (Nery et al., 1982), heart (Zhang et al., 1993), and metabolic diseases (Regensteiner et al., 1985), and are improved by exercise training (Murias, Kowalchuk, & Paterson, 2010). Therefore, it is generally accepted that assessing exercise-onset VO_2 kinetics is a sensitive tool for the specific evaluation of oxidative capacity of skeletal muscle (Grassi, 2006).

3.3.2.2 Secondary outcome measures

Cardiovascular disease (CVD) risk

For estimation of CVD risk, age, blood pressure (Omron, HEM-7131-E, Omron healthcare Europe B.V., Netherlands), body weight (Seca, FysioPlus, Germany) and height (Seca, FysioPlus, Germany) and waist circumference were measured. Blood pressure was measured three times in supine position and was averaged. Body weight was measured once barefoot and 0.5 kilogram was subtracted for clothing weight. Body height was measured once barefoot with feet ten centimeters apart, feet and shoulders against the wall and neutral head position. Furthermore, BMI was calculated from body height and body weight. Waist circumference was measured three times halfway the upper border of the iliac crest and the 12th rib using a tapeline and was averaged.

Past physical activity

Past physical activity was assessed by weekly hours of aerobic sports activity, which was derived by one item of the Baecke questionnaire. This questionnaire consists of 16 items concerning physical activity. Only item nine was considered important to define past physical activity as a possible confounding variable. Scoring was performed on a five-point scale (1 = <1h, 2 = 1-2h, 3 = 2-3h, 4 = 3-4h, 5 = >4h). Other items of the Baecke questionnaire were used to interpret the representativeness of item nine for total physical activity.

Peri-operative course parameters

During hospitalization, following parameters were assessed: hospitalization duration, ICU length of stay, intubation time, peri-operative bleeding, blood C-reactive protein (CRP) concentration and complications.

Others

Medication intake before hospitalization, medical history, comorbidities and smoking behavior/history were requested preoperatively from medical records and a questionnaire compiled by the investigators (added in Dutch in appendix 2).

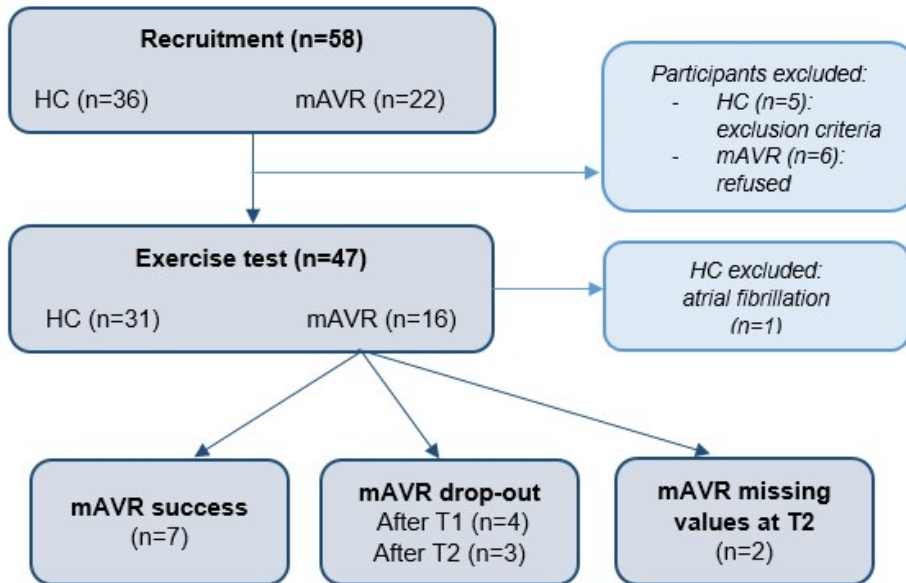
3.3.3 Data analysis

All calculations were performed using SPSS® V. 24.0 (IBM Corporation, USA). Data were expressed as mean±SD. Normal distribution of data was explored by Shapiro-Wilk tests ($p>0.05$). If continuous data were normally distributed, Independent Samples T-Test was used to compare healthy controls with mAVR patients. Repeated Measures Analysis of Variances (ANOVA) was applied to analyze the time effects in mAVR patients. If data remained not normally distributed after logistic transformation, Mann Whitney U, Friedman Test and Wilcoxon Signed Rank Test were applied respectively. Categorical data were analyzed with χ^2 -test or Fisher Exact test. Automatic linear modelling was applied to detect preoperative parameters that predicted significant deterioration in postoperative exercise parameters in mAVR patients. Finally, a multivariate linear regression model was applied to evaluate significant correlations between these preoperative predictors and postoperative parameters of deteriorated exercise capacity. Statistical significance was set at $p<0.05$ (two-tailed). Observed statistical power was calculated for each significant finding using G-power 3.0.10 (Franz Faul, Germany) and was considered sufficient if > 0.80 .

4. RESULTS

4.1 Participants

Thirty healthy controls and 16 mAVR patients were included for data analysis. Further details of recruitment and drop-out are presented in figure 2. During the study course nine patients were not able to perform exercise testing at T2 and/or T3 due to exhaustion.



HC, healthy controls; mAVR, patients undergoing minimal invasive aortic valve replacement

Figure 2 Flowchart study course

Healthy controls matched the mAVR patients for all subject characteristics, except for resting heart rate ($p=0.021$), past physical activity ($p=0.042$), smoking behavior ($p=0.037$) and diuretics intake ($p=0.007$). For further details of subject characteristics, see table 1.

Table 1 Subject characteristics at baseline

Table 1: Subject characteristics at baseline	Healthy controls Mean (\pm SD)	AS (preop) Mean (\pm SD)	Differences between groups $p < 0.05$
n	30	16	
Age (years)	69.6 (\pm 5.1)	68.2 (\pm 12.3)	$p = 0.665$
Males (n)	21	7	$p = 0.116$
Body mass index (kg/m ²)	26.5 (\pm 3.9)	26.6 (\pm 3.9)	$p = 0.935$
Waist circumference (cm)	96.4 (\pm 10.9)	89.4 (\pm 16.8)	$p = 0.100$
Systolic blood pressure (mmHg)	13.8 (\pm 1.4)	14.5 (\pm 2.2)	$p = 0.196$
Diastolic blood pressure (mmHg)	8.3 (\pm 1)	8.0 (\pm 1.2)	$p = 0.401$
HR rest (bpm)	60.6 (\pm 8.6)	68.6 (\pm 12.9)	$p = 0.021$
Past physical activity	2-3h/week (\pm 1)	1-2h/week (\pm 0.5)	$p = 0.043$
Smoking (n)	7 (no), 22 (quit), 1 (yes)	7 (no), 6 (quit), 3 (yes)	$p = 0.037$
Cardioprotective medication intake			
<i>Anticoagulants</i>	9	8	$p = 0.107$
<i>Betablockers</i>	1	2	$p = 0.234$
<i>Antihypertensives</i>	7	6	$p = 0.288$
<i>Antiarrhythmics</i>	1	1	$p = 0.540$
<i>Diuretics</i>	0	4	$p = 0.007$
<i>Cholesterol reducers</i>	10	6	$p = 0.738$

AS, aortic stenosis patients; SD, standard deviation; preop, preoperative

4.2 Perioperative parameters in mAVR patients

Perioperative parameters of the mAVR patients are summarized in table 2. Blood C-reactive protein concentrations significantly increased after surgery ($p = 0.007$).

Table 2 Peri-operative data

Table 2: Perioperative data	Mean (\pm SD)
Hospitalisation duration (days)	6 (\pm 1.5)
Length of ICU stay (hours)	35 (\pm 14)
Duration of mechanical ventilation (hours)	7 (\pm 4)
Perioperative bleeding (ml)	150 (\pm 196)
CRP preop (mg/l)	3.3 (\pm 3.4)
CRP 1 day postop (mg/l)	55.4 (\pm 26.2)
CRP evolution pre-postop	$p = 0.007$

ICU, intensive care unit; CRP, C-reactive protein; preop, preoperative; post-op, postoperative; SD, standard deviation

4.3 Comparison between AS patients and healthy controls

When comparing to healthy controls (see table 3), AS patients showed a significantly higher preoperative MRT (AS 57.4 ± 13.4 s vs. HC 41.2 ± 9.3 s), EqO₂ (AS 31.4 ± 4.6 VE·VO₂⁻¹ vs. HC 26.8 ± 2.6 VE·VO₂⁻¹), EqCO₂ (AS 34.3 ± 5.6 VE·VCO₂⁻¹ vs. HC 31.1 ± 6.2 VE·VCO₂⁻¹), resting HR (AS 68.6 ± 12.9 bpm vs. HC 60.6 ± 8.6 bpm) and lower O₂ pulse (AS 8.3 ± 1.2 ml/beat vs. HC 15.8 ± 3.2 ml/beat) during exercise. Other parameters were not significantly different between both

groups at baseline. All significant results showed an observed power > 0.85, except for EqCO₂ (0.40) and resting HR (0.64).

4.4 Changes in cardiopulmonary exercise capacity after mAVR

At postoperative day five both equivalentents were elevated compared to the preoperative values (EqO₂ (VE·VO₂⁻¹): 38.1±8.1 at T2 vs. 31.4±4.6 at T1 and EqCO₂ (VE·VCO₂⁻¹): 41.1±7 at T2 vs. 34.3±5.6 at T1). Three weeks postoperatively both equivalentents declined compared to postoperative day five, but remained higher than preoperative values (EqO₂ (VE·VO₂⁻¹): 34.3±5.1 at T3, 38.1±8.1 at T2, 31.4±4.6 at T1 and EqCO₂ (VE·VCO₂⁻¹): 36.9±5.5 at T3, 41.1±7 at T2, 34.3±5.6 at T1). Minute ventilation was raised at postoperative day five compared to the preoperative value (27.4±5.6 l/min at T2 vs. 21.8±3.3 l/min at T1). A significantly higher RPE was observed at postoperative day five compared to other time points (11.3±2.3 at T2 vs. 9.8±2.4 at T1 and 10.7±2.7 at T3). Other parameters did not significantly change over time (for further details see table 3). All significant results showed an observed power >0.85, except for change in EqCO₂ from T1 until T3 (0.61) and change in RPE from T1 until T2 (0.63).

Table 3 Data exercise test

Table 3: Data exercise test	Healthy controls (n=30) Mean (± SD)	AS preop (n=16) Mean (± SD)	mAVR early postop 5 days (n=10) Mean (± SD)	mAVR late postop 3 weeks (n=9) Mean (± SD)	Differences between HC and AS p < 0.05	Differences in mAVR between time points p < 0.05		
MRT (seconds)	41.2 (± 9.3)	57.4 (± 13.4)	65.6 (± 10.1)	60 (± 16.2)	T1	p = 0.000	T1-T2	p = 0.424
					T2	p = 0.000	T2-T3	p = 0.521
					T3	p = 0.000	T1-T3	p = 1.000
VE (l/min)	24 (± 4.4)	21.8 (± 3.3)	27.4 (± 5.6)	23.4 (± 5.8)	T1	p = 0.086	T1-T2	p = 0.020
					T2	p = 0.058	T2-T3	p = 0.140
					T3	p = 0.730	T1-T3	p = 1.000
Vt (ml/ breath)	1242.6 (± 324)	1041.6 (± 366.5)	1058.85 (± 192.6)	931.1 (± 243.1)	T1	p = 0.062	T1-T2	p = 0.151
					T2	p = 0.100	T2-T3	p = 0.978
					T3	p = 0.012	T1-T3	p = 0.354
RER	0.89 (± 0.05)	0.92 (± 0.04)	0.92 (± 0.07)	0.93 (± 0.05)	T1	p = 0.072	T1-T2	p = 0.203
					T2	p = 0.200	T2-T3	p = 0.063
					T3	p = 0.020	T1-T3	p = 0.594
EqO ₂	26.8 (± 2.6)	31.4 (± 4.6)	38.1 (± 8.1)	34.3 (± 5.1)	T1	p = 0.001	T1-T2	p = 0.005
					T2	p = 0.000	T2-T3	p = 0.043
					T3	p = 0.002	T1-T3	p = 0.051
EqCO ₂	31.1 (± 6.2)	34.3 (± 5.6)	41.1 (± 7)	36.9 (± 5.5)	T1	p = 0.006	T1-T2	p = 0.005
					T2	p = 0.000	T2-T3	p = 0.024
					T3	p = 0.001	T1-T3	p = 0.008
RPE	9.2 (± 1.6)	9.8 (± 2.4)	11.3 (± 2.3)	10.7 (± 2.7)	T1	p = 0.581	T1-T2	p = 0.036
					T2	p = 0.005	T2-T3	p = 0.639
					T3	p = 0.149	T1-T3	p = 1.000
Lactate (mmol/l)	3.1 (± 0.9)	3 (± 1.6)	3.3 (± 0.9)	3 (± 1)	T1	p = 0.574	T1-T2	p = 1.000
					T2	p = 0.619	T2-T3	p = 1.000
					T3	p = 0.670	T1-T3	p = 1.000
Resting HR (bpm)	60.6 (± 8.6)	68.6 (± 12.9)	73.5 (± 9.5)	70.9 (± 27)	T1	p = 0.021	T1-T2	p = 1.000
					T2	p = 0.000	T2-T3	p = 0.778
					T3	p = 0.354	T1-T3	p = 0.641
%HR	57.4 (± 7.3)	56 (± 8.1)	56.7 (± 4.6)	53 (± 13.9)	T1	p = 0.530	T1-T2	p = 1.000
					T2	p = 0.752	T2-T3	p = 0.172
					T3	p = 0.095	T1-T3	p = 0.066
O ₂ pulse (VO ₂ /HR)	15.8 (± 3.2)	8.3 (± 1.2)	8.2 (± 0.8)	8.4 (± 1.5)	T1	p = 0.000	T1-T2	p = 1.000
					T2	p = 0.000	T2-T3	p = 0.279
					T3	p = 0.000	T1-T3	p = 0.062

mAVR, aortic stenosis patients who underwent minimally invasive aortic valve replacement; HC, healthy controls; SD, standard deviation; AS, patients with aortic stenosis; MRT, mean response time; s, seconds; VE, minute ventilation; Vt, tidal volume; RER, respiratory exchange ratio; EqO₂, ventilator equivalent for oxygen; EqCO₂, ventilatory equivalent for carbon dioxide; RPE, rate of perceived exertion; HR, heartrate; %HR, heart rate percentage; O₂ pulse, oxygen pulse; T1, preoperative; T2, 5 days postoperative; T3, 3 weeks postoperative.

4.5 Predictors for postoperative deterioration of cardiopulmonary function during exercise

Detailed information concerning significant predictors for deterioration of cardiopulmonary function during exercise is summarized in table 4. All correlations showed an observed power ≥ 0.99 .

4.5.1 Predictors for deterioration of cardiopulmonary function during exercise at five postoperative days

Preoperative EqCO₂ was the only significant predictor for EqO₂ at five days after surgery and showed a positive correlation (SC = 0.735, p = 0.012). Furthermore preoperative RER and perioperative mechanical ventilation time were negatively correlated with Ve at five days (SC = -0.491, p = 0.019 ; SC = -0.748, p = 0.002 respectively). No other significant predictors were found.

4.5.2 Predictors for deterioration of cardiopulmonary function during exercise at three postoperative weeks

EqO₂ at three weeks was significantly predicted by preoperative O₂ pulse, BMI, Ve and Vt, showing a negative correlation for BMI, Ve and Vt (SC = -0.590, p = 0.000 ; SC = -0.346, p = 0.003 ; SC = -0.262, p = 0.003 respectively) and a positive correlation for O₂ pulse (SC = 1.083, p = 0.000). Also EqCO₂ at three weeks was positively correlated with preoperative O₂ pulse (SC = 0.742, p = 0.001) and was negatively correlated with gender (SC = -0.336, p = 0.045).

Table 4 Multivariate linear regression

Table 4: Multivariate linear regression		
Follow-up exercise parameters		Significant predictors
EqO2	5 days	Adjusted R² = 0.725 Exercise EqCO2 (SC = 0.735, p = 0.012)
	3 weeks	Adjusted R² = 0.994 Exercise O2 pulse (SC = 1.083, p = 0.000) BMI (SC = -0.590, p = 0.000) Exercise Ve (SC = -0.346, p = 0.003) Exercise Vt (SC = -0.262, p = 0.003)
EqCO2	5 days	<i>No significant predictors found</i>
	3 weeks	Adjusted R² = 0.897 Exercise O2 pulse (SC = 0.742, p = 0.001) Gender (SC = -0.336, p = 0.045)
RPE	5 days	<i>No significant predictors found</i>
Ve	5 days	Adjusted R² = 0.764 Ventilation time (SC = -0.748, p = 0.002) Exercise RER (SC = -0.491, p = 0.019)

Significance level: $p < 0.05$; SC, Standardized Coefficients Beta; EqO2, ventilator equivalent for oxygen; EqCO2, ventilatory equivalent for carbon dioxide; RPE, rate of perceived exertion; Ve, minute ventilation; O2 pulse, oxygen pulse; BMI, body mass index; Vt, tidal volume; RER, respiratory exchange ratio.

5. DISCUSSION

This study showed, as expected, a reduced cardiopulmonary exercise tolerance in patients with severe aortic stenosis as opposed to healthy controls. However, after minimally invasive aortic valve replacement through hemi-sternotomy, in contrast to the suspected improvement, a deterioration in exercise tolerance was observed.

A significant greater MRT in patients with severe aortic stenosis was found as opposed to healthy controls, which assumes worse exercise-onset VO_2 kinetics in the patient group (Arena, Humphrey, Peberdy, & Madigan, 2003). A multifactorial cause for this phenomenon can be hypothesized. First, a dysfunctional oxygen uptake at the site of the skeletal muscle itself can impair this process (Grassi, 2006). However no elevated lactate values were observed within the aortic stenosis group compared to the healthy controls ($p > 0.05$). This thus presumes a normal skeletal muscle metabolism. However, a greater MRT can also be a consequence of failing of the cardiopulmonary system to provide enough oxygen (Tschakovsky & Hughson, 1999). In severe aortic stenosis, a lower cardiac output and subsequent lower oxygen pulse, which was observed in the patient group ($p < 0.05$), can be caused by the resistance of the stenotic valve (Lee, Jonsson, Bevegård, Karlöf, & Aström, 1970). This dysfunctional process may induce lower perfusion of the lung capillaries, leading to less efficient gas exchange, resulting in ventilation-perfusion mismatch (Aubier, Trippebach, & Roussos, 1981, as cited in Shenkman, Shir, Weiss, Bleiberg, & Gross, 1997). This ventilation-perfusion mismatch could explain why MRT is higher in AS patients (Chatterjee et al, 2012). The higher ventilatory equivalents for CO_2 and O_2 indeed support this hypothesis.

After mAVR, the MRT and oxygen pulse did not improve during the first three postoperative weeks and was accompanied by further impairment of ventilatory equivalents for CO_2 and O_2 . This assumes a deterioration of exercise tolerance and gas exchange efficiency. Similar findings are supported by the current literature in patients up to one year after cardiac surgery (Asimakopoulos et al, 1999; Shenkman et al, 1997; Westerdahl, Jonsson, & Emtner, 2016). Dysfunctional pulmonary gas exchange after cardiac surgery is often accompanied by an elevated alveolar-arterial oxygen difference, causing an oxygenation defect (Matthey & Wiener-Kronish, 1989). Several hypotheses can be formulated to explain these pulmonary

dysfunctions. First, it should be considered that after mAVR, cardiopulmonary dysfunction is not immediately restored. Previous studies already showed maintained dysfunction of the cardiopulmonary system after aortic valve replacement in terms of impaired cardiac output and elevated filling pressures (Zhao, Henein, Mörner, Gustavsson, Holmgren, & Lindqvist, 2011). Zhao et al (2011) hypothesizes that this finding is potentially related to myocardial fibrosis and incomplete recovery of left ventricular hypertrophy. This postoperative cardiopulmonary inefficiency to provide enough oxygen can maintain the previously hypothesized ventilation-perfusion mismatch and the subsequent higher MRT. Second, an elevated pulmonary and systemic inflammatory reaction in response to cardiac surgery can result in postoperative pulmonary dysfunction, which is expressed in impaired gas exchange and changes in lung mechanisms (Badenes, Lozano, & Belda, 2015). Inflammatory reactions can remain subclinical and may be provoked by general anesthesia, topical cooling for myocardial protection and cardiopulmonary bypass (Asimakopoulos, Smith, Ratnatunga, & Taylor, 1999; Birdi et al, 1996; Hedenstierna, Strendberg, Brismar, Lundquist, Svensson, & Tokics, 1985). This study showed an elevation in blood C-reactive protein (CRP) concentration after mAVR ($p = 0.007$). However, no correlations between inflammatory markers (CRP) and ventilatory equivalents were found. Third, pulmonary edema is a possible side effect after use of cardiopulmonary bypass and is a plausible cause of impaired ventilation-perfusion (Tennenberg, Clardy, Baily, & Solomkin, 1990; Weissman, 2004). However, retrieval of medical imaging of the mAVR patients in this study did not reveal pulmonary edema. Finally, biological (inflammatory response) and mechanical (baro- and volutrauma) damage from suboptimal mechanical ventilation can result in anatomical damage of the lung epithelial structures, local and systemic inflammatory reactions and impaired gas exchange (Badenes, Lozano, & Belda, 2015). However, detailed information concerning mechanical ventilation settings are not available, therefore a conclusion concerning this hypothesis is difficult to draw. As the cause of the higher MRT can presumably be related to maintained cardiopulmonary impairment after surgery, physical therapists should emphasize on early cardiopulmonary rehabilitation. Moreover, early detection of aortic valve stenosis is important as the ongoing abnormalities seem to be related to progressive myocardial fibrosis and left ventricular hypertrophy. Furthermore, efforts should be made to maintain the inflammatory body state at the lowest level, for example by reducing cardiopulmonary bypass

time or by avoiding this bypass at all. Another clinical implication is to optimize the settings of mechanical ventilation to reduce its disadvantageous effects.

Another time effect was an elevation of minute ventilation after surgery, which could serve as a pulmonary compensation for the ventilation-perfusion mismatch. This elevation can be supported by the demonstrated positive correlation between preoperative V_e and V_t , and the postoperative ventilatory equivalent for O_2 . A last observed time effect was an elevation in rate of perceived exertion only five days after surgery, which can be explained by fatigueness from surgery and the previously shown decreased cardiopulmonary tolerance.

Some interesting correlations were found in this study. A greater deterioration of ventilatory equivalent for CO_2 at three weeks after surgery was found in males. Contrary, the current literature shows worse pulmonary function during exercise in healthy females, compared to males (Harms, 2006). Furthermore, worse outcome (30 day mortality) in females is confirmed in a mAVR population (Katz et al, 2017). Thus, due to this conflicting evidence, a straightforward conclusion concerning gender effect is difficult to draw. As supported by other studies, patients with a higher BMI showed less pulmonary deterioration in this study. Chase et al (2008) show similar results in the heart failure population, more specifically a negative correlation between BMI and ventilatory equivalent for CO_2 . This phenomenon is currently named as 'the obesity paradox' (Takagi, Umemoto, &ALICE Group, 2017). Noteworthy, worse ventilatory equivalents for CO_2 and O_2 were according to this study also predicted by better preoperative oxygen pulse. Another remarkable correlation was found between lower preoperative RER and higher minute ventilation at three weeks after surgery. However, a reasonable explanation for these two observations cannot be provided by the authors, neither by current literature. Finally, shorter perioperative ventilation time was predictive for postoperative deterioration in minute ventilation during exercise. Conflicting evidence is reported in a previous study which shows a deterioration in pulmonary function after longer mechanical ventilation time in patients after cardiovascular surgery (Rady, Ryan, &Starr, 1997). Consequently, clinical considerations are difficult to state. Surely, attention should be given to BMI as soon as possible in terms of preservation and/or elevation of lean tissue mass.

Several important limitations of this study should be taken into account when drawing a conclusion concerning the results. First, healthy controls and mAVR patients were not matched for physical activity, smoking behavior and diuretic use, which may induce confounding bias. Second, a high amount of missing data within patients and within follow-up were present, which further lowers the amount of available data. Furthermore, the algebraically calculation of MRT is validated in healthy subjects, but may not be valid in this aortic stenosis population (Arena, Humphrey, Peberdy, & Madigan, 2003). However, such validation study is practically impossible, due to the need of a maximal exercise test, which is harmful in this critical population. An alternative in terms of muscle biopsy can be a solution to this problem, but would take years to investigate. Moreover, muscle biopsy in addition to lactate measurement would give more profound information on the mechanisms behind the elevated MRT. Remarkably, despite the small sample sizes used in this study, statistical power analysis frequently revealed high observed power concerning significant findings. However, for evaluating changes over time of two exercise parameters in mAVR patients (i.e. EqCO₂ and RPE), sample size should have reached a number of 25 and 23 respectively, to achieve sufficient statistical power (> 0.80). The final conclusion of this study should therefore be drawn with caution.

Future research should emphasize on larger sample sizes for investigating certain outcomes (i.e. EqCO₂ and RPE) during exercise in patients undergoing mAVR. Moreover, effects of exercise tolerance after mAVR in the long term need to be explored and subsequent prescribed rehabilitation programs should be tested for their effectiveness. This last consideration will be investigated during the continuation of this study. Also, attention should be paid to more pre- and perioperative prognostic variables for cardiopulmonary deterioration during exercise.

In conclusion, lower exercise tolerance in patients with severe aortic stenosis was not improved after mAVR, but even more deteriorated in the short term. Long term follow-up and evaluation of cardiopulmonary rehabilitation programs are necessary to achieve better outcome.

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Appendix 1



Photo 1 View on the aorta through hemi-sternotomy with 4-5 cm incision. Retrieved from “Minimally invasive aortic valve replacement” from Jessa Hospital, Cardiac Surgery, 2015 (<http://www.cardiothoracalechirurgie.be/professionals/minimally-invasive-aortic-valve-replacement>). Taken with permission 2015, Jessa Hospital, Cardiac Surgery.

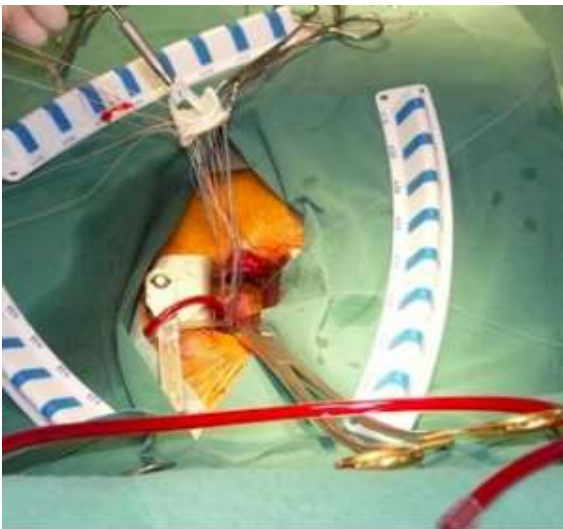


Photo 2 Placement of the artificial valve with parachute technique. Retrieved from “Minimally invasive aortic valve replacement” from Jessa Hospital, Cardiac Surgery, 2015 (<http://www.cardiothoracalechirurgie.be/professionals/minimally-invasive-aortic-valve-replacement>). Taken with permission 2015, Jessa Hospital, Cardiac Surgery.

Appendix 2

Naam: Voornaam:

Datum: Lengte: Gewicht:

Beste meneer/mevrouw,

Hieronder volgen enkele vragen in verband met uw medicatiegebruik en algemene gezondheidstoestand. Gelieve tijdens de eerste afname van de vragenlijst (voor de operatie) uw juiste antwoorden aan te kruisen in de kolom 'VOOR'. Tijdens de derde afname (1 maand na de operatie) kan u hetzelfde doen in de kolom 'NA'. Tijdens de tweede afname (bij ontslag) hoeft u alleen de vragen op pagina 3 in te vullen. Alvast bedankt!

Bent u een gezonde controle, hoeft u deze vragenlijst slechts één maal in te vullen. Gelieve uw antwoorden aan te kruisen in de kolom 'VOOR'.

Gebruikt u één of meerdere van onderstaande geneesmiddelen? Gelieve deze aan te kruisen.	VOOR	NA
Bloedverduuners (bv. Marcoumar, Sintrom, Asprine, Plavix, ...)		
Bèta-blokkers (bv. Emlor, Seloken, Propranolol, Atenolol, Nebilet, Eucardic, ...)		
Bloeddrukverlagende middelen (bv. Acupril, Capoten, Coversyl, Titrace, Zestril, ...)		
Anti-aritmica (bv. Sotacor, Cordarone, Tambocor, ...)		
Diuretica (bv. Burinex, Lasix, Aldacton, ...)		
Cholesterolverlagende middelen (bv. Zocor, Selektine, Lipitor, Crestor, ...)		
Antibiotica		
Pijnstillers (bv. Dafalgan, Paracetamol, Perdolan Codeine, morfine, ...)		
Ontstekingsremmers (bv. Brufen, Voltaren, Diclofenac, ...)		
Ander:		
Lijdt u aan één of meerdere van onderstaande aandoeningen? Gelieve deze aan te kruisen.	VOOR	NA
Diabetes type 1 of 2		
COPD, astma of andere longaandoening (welke?))		
Reuma		
Eerdere hartaandoening of hartoperatie (welke?))		

Andere:		
Wat is uw rookgedrag?	VOOR	NA
Ik heb nooit gerookt		
Ik ben gestopt met roken (hoelang? weken/maanden/jaren (onderlijn))		
Ik rook op dit moment		

Voor de operatie / gezonde controle

Noteer hieronder per geneesmiddel hoe vaak u deze inneemt:

Vb. Dafalgan – 3x/dag, Marcoumar – 1x/dag

.....
.....
.....
.....

Beschrijf hieronder uw fysieke activiteit: welke activiteiten, hoe veel keer per week,...

Vb. 5 km fietsen, 2x/week ; 10 km wandelen, 1x/week ; 200m te voet naar de winkel, 3x/week

.....
.....
.....
.....

Heeft u op dit moment ergens last van (eender wat?) Beschrijf.

.....
.....
.....
.....

Wat heeft u vandaag reeds gegeten en op welke tijdstippen?

.....
.....
.....
.....

5 dagen na de operatie (enkel deze vragen in te vullen voor fietsproef, niet de tabel)

Heeft u op dit moment ergens last van (eender wat?) Beschrijf.

.....
.....
.....
.....

Wat heeft u vandaag reeds gegeten en op welke tijdstippen?

.....
.....
.....
.....

3 weken na de operatie

Noteer hieronder per geneesmiddel hoe vaak u deze inneemt:

Vb. Dafalgan – 3x/dag, Marcoumar – 1x/dag

.....
.....
.....
.....

Beschrijf hieronder uw fysieke activiteit: welke activiteiten, hoe veel keer per week,...

Vb. 5 km fietsen, 2x/week ; 10 km wandelen, 1x/week ; 200m te voet naar de winkel, 3x/week

.....
.....
.....
.....

Heeft u op dit moment ergens last van (eender wat?) Beschrijf.

.....
.....
.....
.....

Wat heeft u vandaag reeds gegeten en op welke tijdstippen?

.....
.....
.....
.....

Ik, ondergetekendeverklaar hierbij dat ik deze vragenlijst eerlijk en zo getrouw mogelijk heb ingevuld.

Datum:

Handtekening:

.....

.....

Auteursrechtelijke overeenkomst

Ik/wij verlenen het wereldwijde auteursrecht voor de ingediende eindverhandeling:
Significant deterioration of cardiopulmonary exercise tolerance after minimally invasive aortic valve replacement

Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij kinderen**
Jaar: **2017**

in alle mogelijke mediaformaten, - bestaande en in de toekomst te ontwikkelen - , aan de Universiteit Hasselt.

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Vanderlinden, Maartje

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