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The effect of minimally invasive surgical aortic valve replacement on postoperative pulmonary and skeletal muscle function

Hajar Boujemaa[1] | Alaaddin Yilmaz[2] | Boris Robic[2] | Katrien Koppo[3] | Guido Claessen[4,5] | Ines Frederix[1,4,6] | Paul Dendale[1,4] | Heinz Völler[7] | Luc JC van Loon[8] | Dominique Hansen[1,4]

[1]BIOMED – Biomedical Research Center, and REVAL – Rehabilitation Research Center, Faculty of Medicine and Life Sciences, Faculty of Rehabilitation Sciences, Hasselt University, Diepenbeek, Belgium

[2]Jessa Hospital, Department of Cardiothoracic Surgery, Hasselt, Belgium

[3]Exercise Physiology Research Group, Department of Movement Sciences, KU Leuven, Leuven, Belgium

[4]Jessa Hospital, Heart Centre Hasselt, Hasselt, Belgium

[5]University Hospitals Leuven, Leuven, Belgium

[6]Faculty of Medicine and Health Sciences, Antwerp University, Antwerp, Belgium

[7]Humanwissenschaftliche Fakultät, Universität Potsdam, Potsdam, Germany

[8]Department of Human Biology, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre, Maastricht, the Netherlands

Correspondence
Dominique Hansen, Hasselt University, Faculty of Rehabilitation Sciences, Agoralaan, Building A, 3590 Diepenbeek, Belgium.
Email: Dominique.hansen@uhasselt.be

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Abstract

Suboptimal post-operative improvements in functional capacity are often observed after minimally invasive aortic valve replacement (mini-AVR). It remains to be studied how AVR affects the cardiopulmonary and skeletal muscle function during exercise to explain these clinical observations and to provide a basis for improved/tailored post-operative rehabilitation. Twenty-two patients with severe aortic stenosis (AS) (aortic valve area (AVA) <1.0 cm^2) were pre-operatively compared to 22 healthy controls during submaximal constant-workload endurance-type exercise for oxygen uptake ($\dot{V}_{O_2}$), carbon dioxide output ($\dot{V}_{CO_2}$), respiratory gas exchange ratio, expiratory volume ($\dot{V}_E$), ventilatory equivalents for O_2 ($\dot{V}_E/\dot{V}_{O_2}$) and CO_2 ($\dot{V}_E/\dot{V}_{CO_2}$), respiratory rate (RR), tidal volume (V_t), heart rate (HR), oxygen pulse ($\dot{V}_{O_2}$/HR), blood lactate, Borg ratings of perceived exertion (RPE) and exercise-onset $\dot{V}_{O_2}$ kinetics. These exercise tests were repeated at 5 and 21 days after AVR surgery ($n = 14$), along with echocardiographic examinations. Respiratory exchange ratio and ventilatory equivalents ($\dot{V}_E/\dot{V}_{O_2}$ and $\dot{V}_E/\dot{V}_{CO_2}$) were significantly elevated, $\dot{V}_{O_2}$ and $\dot{V}_{O_2}$/HR were significantly lowered, and exercise-onset $\dot{V}_{O_2}$ kinetics were significantly slower in AS patients *vs.* healthy controls ($P < 0.05$). Although the AVA was restored by mini-AVR in AS patients, $\dot{V}_E/\dot{V}_{O_2}$ and $\dot{V}_E/\dot{V}_{CO_2}$ further worsened significantly within 5 days after surgery, accompanied by elevations in Borg RPE, $\dot{V}_E$ and RR, and lowered V_t. At 21 days after mini-AVR, exercise-onset $\dot{V}_{O_2}$ kinetics further slowed significantly ($P < 0.05$). A decline in pulmonary function was observed early after mini-AVR surgery, which was followed by a decline in skeletal muscle function in the subsequent weeks of recovery. Therefore, a tailored rehabilitation programme should include training modalities for the respiratory and peripheral muscular system.

KEYWORDS
aortic valve stenosis, exercise tolerance, surgery

1 | INTRODUCTION

Aortic stenosis (AS) is a chronic, progressive valve disease and the most frequently acquired heart valve disease in Europe (Iung et al., 2003). The prevalence of AS increases up to ∼12% in subjects >75 years of age (Osnabrugge et al., 2013). Due to an ageing population in the Western countries, together with a progressive worsening in cardiovascular risk profile on a population scale, it is expected that the number of patients with AS will progressively increase. Patients usually remain asymptomatic in mild AS (Rosenhek et al., 2000), while more severe AS is accompanied by various secondary (e.g. increased left ventricular myocardial mass) and primary (e.g. chest pain, shortness of breath, syncope) symptoms (Vahanian et al., 2012). If not treated, the estimated 5-year survival of severe (symptomatic) AS is only 15–50% (Vahanian et al., 2012). As a result, the anticipated rise in AS prevalence will have an increased impact on public health and healthcare consumption as well as quality of life of the older population.

The only effective treatment of severe AS is surgical replacement of the aortic valve (sAVR) or percutaneous transluminal aortic valvuloplasty (Vahanian et al., 2012), leading to significant reductions in morbidity and mortality (Brown et al., 2008; Shan, Saxena, McMahon, Wilson, & Newcomb, 2013). sAVR, executed approximately 275,000 times per year worldwide (Bonow et al., 2008), is performed via a full sternotomy in combination with cardiopulmonary bypass (Schmitto, Mohr, & Cohn, 2011). However, minimally invasive AVR (mini-AVR) (Bonow et al., 2008) has been performed more often during the past decade and has emerged as a promising new treatment strategy for high-risk patients, because this procedure results in a lesser inflammatory response, less pain and blood loss, lowered infection risk, a better cosmetic result, shorter intubation time and shorter hospital stay (Falcone et al., 2014; Higgins et al., 2011; Lindman et al., 2015). The better stability of the sternum and thorax with mini-AVR also leads to improvement of the patient's respiratory function and earlier mobilization translating into shorter mechanical ventilation support (Doll et al., 2002). Moreover, mini-AVR is associated with a better prognosis as opposed to transcatheter aortic valve replacement (TAVI) (Takagi, 2016). Due to these clinical advantages, it is anticipated that mini-AVR will be performed more frequently (Ando, Takagi, & Grines, 2017; Myles, 2014; Pope, 2014).

To improve sAVR success rates and optimize post-operative care/treatment, studies examine patients' outcomes but very often focus on hard endpoints only (e.g. adverse cardiovascular events and mortality) (Ando et al., 2017). Softer endpoints (e.g. quality of life, relief of symptoms and recovery) and functional outcome parameters should also be considered during follow-up after cardio-thoracic surgery (Myles, 2014), as this makes earlier and/or tailored intervention possible in case of anomalous recovery, even before onset of symptoms, potentially leading to improved patient outcomes.

Although currently not implemented as standard in daily clinical practice, cardiopulmonary exercise testing (CPET) could be performed preferably early after mini-AVR. For example, some CPET parameters (such as a lower peak oxygen uptake ($\dot{V}_{O_2 peak}$) and O_2 pulse) predict a worse outcome in AS patients when compared to patients with normal responses (Alborino, Hoffmann, Fournet, & Bloch, 2002; Dhoble et al., 2014; Dulgheru et al., 2013; Le, Jensen, & Kjoller-Hansen, 2017; Levy, 2014). Moreover, to gain insights in post-operative recovery following sAVR and to asses when and where issues develop, CPET testing should be performed preferably early after sAVR. Many CPET parameters can provide greater insights into the cardiac, pulmonary and skeletal muscle responses of the patient. Such early systematic follow-up after sAVR may thus lead to a greater understanding of how post-operative recovery is manifested and which additional and/or tailored interventions could be implemented to improve this recovery. This may be highly relevant as suboptimal post-operative improvements in functional capacity were observed in a significant number of patients who had sAVR (Munt et al., 1997) or TAVI (Abdul-Jawad Altisent et al., 2017). However, in these studies, a relatively late follow-up screening was performed (several months after surgery). In addition, changes in pulmonary and muscular function during exercise remain to be studied.

The aim of this exploratory study is therefore to examine, for the first time, changes in cardiopulmonary and skeletal muscle function during endurance exercise early after mini-AVR to obtain a greater understanding of how recovery in these systems is manifested and, if needed, to reveal the need for optimization of post-operative treatment specifically for patients undergoing mini-AVR. In this study, it is shown that despite the successful restoration of the aortic valve area by mini-AVR, the post-operative treatment should be optimized to specifically improve pulmonary and skeletal muscle function during exercise, and this within different time frames after surgery. These data may further highlight the importance of multidisciplinary follow-up and treatment, such as rehabilitation.

New Findings

- **What is the central question of this study?**
  How does surgical aortic valve replacement affect cardio-pulmonary and muscle function during exercise?
- **What is the main finding and its importance?**
  Early after the surgical replacement of the aortic valve a significant decline in pulmonary function was observed, which was followed by a decline in skeletal muscle function in the subsequent weeks of recovery. These date reiterate, despite restoration of aortic valve function, the need for a tailored rehabilitation programme for the respiratory and peripheral muscular system.

2 | METHODS

2.1 | Ethical approval

The institutional ethical board at Jessa Hospital (Hasselt, Belgium) and Hasselt University (Hasselt, Belgium) approved the research protocol of this study, which conformed to the standards set by the *Declaration of Helsinki* (protocol number: B243201629467). Signed informed consents of all healthy individuals and AS patients were obtained after explaining the aim, risks and benefits of this study. This study was not *a priori* registered.

2.2 | Study design

This was a prospective cross-sectional (first part) and longitudinal (second part) study. First, cardiopulmonary and skeletal muscle function during constant-workload endurance-type exercise were compared between 22 patients with severe AS and 22 healthy sex-, body mass index (BMI)- and age-matched controls without aortic

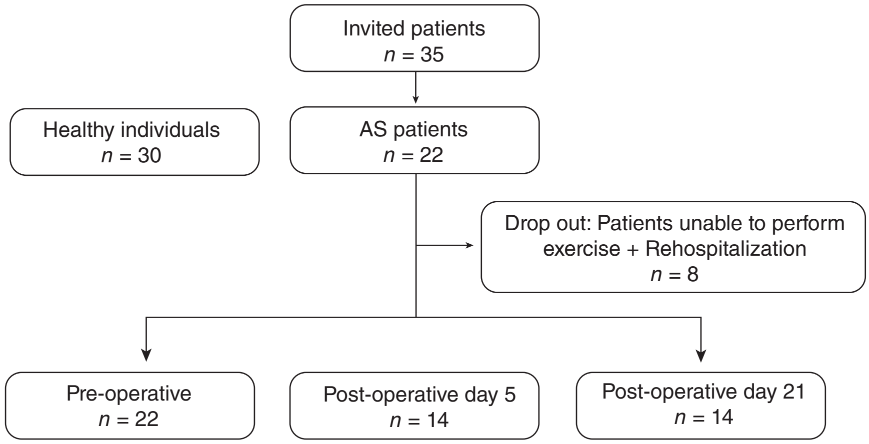

FIGURE 1 Flowchart of AS patient population and healthy controls

stenosis. Such comparison was mandatory as there are no reference values for the collected cardiopulmonary parameters during this specifically designed exercise test. Second, changes in pulmonary and skeletal muscle function during constant-workload exercise were examined in AS patients at 5 and 21 days after mini-AVR. In addition, changes in cardiac function were assessed by echocardiography at rest at similar time points.

2.3 | Subjects

Twenty-two patients with AS (from 35 invitees) and 22 healthy individuals, without AS, matched for age, sex and BMI, participated in this study (see Figure 1). The AS patients had to be diagnosed with severe AS (aortic valve area (AVA) < 1.0 cm^2), without a presence or history of coronary artery or peripheral arterial disease. Within 21 days of post-operative follow-up, eight patients were no longer able to execute the exercise test due to excessive dyspnoea ($n = 4$) or were re-hospitalized ($n = 4$).

2.4 | Assessments

2.4.1 | Cardiovascular disease risk

To assess cardiovascular disease risk, blood pressure, body weight and height [from which BMI is calculated by weight (kg)/height (m)^2] and waist circumference was measured after an overnight fast. After a 5 min supine rest, blood pressure and heart rate were measured three times automatically (Omron, HEM-7131-E, Omron Healthcare Europe B.V., Hoofddorp, Netherlands) with averaging of the results, followed by the collection of a blood sample for analysis of lipid profile, blood c-reactive protein and glucose concentration (in AS patients only). Body weight was measured on a digital weight scale (Seca, Birmingham, UK) and body height by a wall-mounted meter (Seca).

2.4.2 | Exercise testing

Subject were advised to eat a light meal 2 h prior to testing and not to perform any exercise the day before or on the day of testing. Subjects performed a submaximal cardiopulmonary exercise test (S-CPET) on an electronically braked cycle ergometer (eBike Basic, General Electric GmbH, Bitz, Germany), consisting of three 6 min exercise bouts at 25% of the predicted peak workload capacity (W_{peak}) (Jones, Makrides, Hitchcock, Chypchar, & McCartney, 1985), interspersed by 6 min no-exercise recovery intervals (sitting on the bicycle at rest) (Hansen, Wens, Kosten, Verboven, & Eijnde, 2013). This workload was selected as we expected a (very) low peak exercise capacity in AS patients.

A breath-by-breath analysis device with a mass spectrometer and volume turbine system (Jaeger Oxycon Pro, Erich Jaeger GmbH, Germany) was used to continuously measure pulmonary gas exchange. Furthermore, oxygen uptake ($\dot{V}_{O_2}$, ml min^{-1}), carbon dioxide output ($\dot{V}_{CO_2}$, l min^{-1}), breathing frequency (BF, breaths min^{-1}), and expiratory volume ($\dot{V}_E$, l min^{-1}), averaged for every 10 s, were assessed breath-by-breath. From these parameters, respiratory gas exchange ratio (RER) and equivalents for O_2 ($\dot{V}_E/\dot{V}_{O_2}$) and CO_2 ($\dot{V}_E/\dot{V}_{CO_2}$) (ventilatory equivalents) were calculated. In addition, $W/\dot{V}_{O_2}$ during the final minute of constant-workload exercise was calculated. Heart rate (HR) was continuously monitored by a 12-lead electrocardiograph device, from which O_2 pulse ($\dot{V}_{O_2}$/HR, ml beat^{-1}) was calculated.

Subjects were seated on a bicycle for 3 min to obtain resting data, followed by the first 6 min exercise bout. After 6 min of cycling, subjects remained seated on the bicycle without pedalling for an additional 6 min after which a second and a third exercise bout was initiated intercepted by 6 min rest.

Following each exercise bout, capillary blood samples were obtained from a fingertip to analyse blood lactate concentrations (mmol l^{-1}), using a portable lactate analyser (Accutrend plus, Roch Diagnostic Limited, Burgess Hill, UK). Ratings of perceived exertion (RPE) were recorded at the end of the constant-load boats using the 15 point graded category scale of Borg.

2.5 | Exercise-onset $\dot{V}_{O_2}$ kinetics

The raw breath-by-breath $\dot{V}_{O_2}$ data from each test were initially examined to exclude errant breaths caused by coughing, swallowing, sighing, etc. and those values lying more than 4 standard deviations from the local mean were deleted (Koppo et al., 2009). Subsequently, these data were linearly interpolated to give 1 s values. For each subject and each exercise condition, the three repetitions of each work rate were time-aligned to the start of exercise, superimposed and ensemble averaged to reduce the breath-to-breath noise and enhance the underlying physiological response characteristics. The baseline $\dot{V}_{O_2}$ was defined as the average $\dot{V}_{O_2}$ measured between 150 and 30 s before the start of exercise. As none of the transitions evidenced a slow component, each averaged response was described using a single exponential model with the following equation (Whipp, Ward, Lamarra, Davis, & Wasserman, 1982):

$$\dot{V}_{O_2}\ (t) = \dot{V}_{O_2\ \text{baseline}} + A\left(1 - e^{-(t-T_d)/\tau}\right)$$

This model includes an amplitude (A), a time constant (T), and a delay time (T_d), which were determined using a non-linear least-square algorithm. The initial cardiodynamic component was ignored by eliminating the data from the first 20s after the onset of exercise.

2.5.1 | Transthoracic echocardiography

A GE Vivid 9 portable Ultrasound Machine (GE Healthcare, Milwaukee, WI, USA) was used to evaluate the cardiac function of AS patients before and after surgery. Transthoracic echocardiography (TTE) with tissue Doppler was executed by the same cardiologist throughout the entire study with the patient in the left lateral decubitus position. A GE M4S Matrix Array sector transducer (GE Healthcare) was used to obtain several images of the heart. The TTE protocol included visualization of the subcostal four-chamber view, apical four-chamber view, apical two-chamber view, and parasternal long-axis and short axis view. A Simpson's rule algorithm was used to estimate EF where apical four- and two-chamber views were analysed. Left-ventricular (LV) systolic and diastolic function was assessed using the following parameters: ejection fraction (EF), LV septum width (mm), LV diameter (mm), left-atrial (LA) diameter (mm), trans-mitral peak early diastolic velocity [E_{mitral} (cm s^{-1})], trans-mitral peak late diastolic velocity [A_{mitral} (cm s^{-1})], mitral E/A ratio, deceleration time [DT (s)], E/E' ratio (E' = early diastolic mitral annular velocity) and cardiac output [CO (l min^{-1})]. LV septum width, LV diameter and LA diameter were assessed on the parasternal long axis (PLAX). E_{mitral}, A_{mitral}, DT, CO and cardiac output index (COi) were evaluated on the apical four-chamber view. Moreover, pulmonary hypertension (pulmonary artery pressure; PAP) and AVA were also analysed in patients before and after mini-AVR surgery with TTE.

2.5.2 | Past physical activity

Past physical activity was evaluated by using the Baecke questionnaire, which measures a person's habitual physical activity related to household activities, transportation, sports, labour activities and sitting time (Hertogh, Monninkhof, Schouten, Peeters, & Schuit, 2008).

2.5.3 | Mini-AVR procedure

Anesthetic management. Patients received standard premedication (diazepam 10 mg) 1 h before arrival to the operating room. Induction of anaesthesia was performed with intravenous sufentanyl and propofol. Muscle relaxation was achieved with pancuronium (0.1 mg kg^{-1}). Anaesthesia was maintained with a combination of propofol (2–3 mg kg^{-1} h^{-1}) and isoflurane. A full dose of heparin (300 IU kg^{-1} intravenously) was given and activated clotting time was maintained above 400 s. On completion of the procedure, heparin was reversed with protamine at 1:1 equivalent dosage.

Cardiopulmonary bypass. Maquet HL30 heart lung machines (Maquet Cardiopulmonary, Hirrlingen, Germany) were used. Minimal extracorporeal circulation (MECC) consisted of a totally closed Bioline heparin coated system circuit with rotaflow centrifugal pump, Quadrox-i microporous membrane oxygenator and venous bubble trap (VBT) (Maquet Cardiopulmonary). A blood collection reservoir connected to the VBT was integrated in the circuit. No open venous reservoir was present. Autologous retrograde priming of the MECC was performed, reducing priming volume to 250 ml. Cell saver drainage was used for intrapericardial bloodshed. A pulmonary artery vent (DLP catheter 13 Fr, Medtronic Inc., Minneapolis, MN, USA) was inserted via the main pulmonary trunk distal to the pulmonary valve. Optional sump suction directly through the aortotomy was used when necessary. The pulmonary artery vent was directly connected to the venous bubble trap maintaining the same level of vacuum suction. The aortic root vent ran via a drip chamber and was also connected to the venous bubble trap. Continuous CO_2 field flooding (6 l min^{-1}) was maintained during the entire procedure. Antegrade warm blood cardioplegia (1.7 mmol ml^{-1} potassium) was administered via the aortic root and repeated every 15–20 min thereafter selectively via the coronary ostia. Nasopharyngeal temperature was kept at 34°C.

Surgical procedure. Minimal access AVR using MECC was performed. The patient was in a supine position with access to the groin for arterial and venous femoral cannulation. A 4–5 cm median, subjugular skin incision was performed in the upper sternal region. This was followed by a J-shaped partial sternotomy into the right third intercostal space, performed with an oscillating saw. First insertion of an appropriately sized femoral artery cannula (Medtronic Inc.) using the Seldinger technique was performed. This was followed by the insertion of a dual stage venous 21 to 25 Fr cannula (Medtronic Inc.) under TTE.

2.5.4 | In-hospital rehabilitation

During hospital stay, all patients received similar physiotherapy intervention. This intervention started in the intensive care unit (ICU) once the patient was able to cooperate (awake and extubated), blood pressure and heart rate were stable, and evidence of myocardial ischaemia or malignant cardiac arrhythmias were absent. In general, patients remained 2–4 days in the ICU. During this intervention, the patient learned deep breathing exercises for a duration of 15 min day^{-1} (with expectoration of mucus when needed) and was gradually mobilized (brought to sitting and standing, and walking for a few metres in the room). In addition, a range of motion exercises for the legs were executed in bed and in chair. Patients also received a respiratory device for autonomic respiratory exercises during the entire hospital stay, and were advised to execute exercise at least twice a day. When the patient was discharged from the ICU and moved to a regular room, endurance exercises (walking in a corridor, cycling against resistance on an ergometer at 60–70 rpm, and arm cranking without applied resistance at 60–80 rpm) up to 30 min day^{-1} at a low intensity (exercise HR < 120 beats min^{-1}) were added on top of the breathing exercises and leg strength exercises. The walking distance and cycling resistance was gradually increased, with the aim to mobilize the patient.

2.5.5 | Statistical analyses

The data analyses were performed in SPSS version 24.0 (IBM Corp., Armonk, NY, USA) and Prism 6.01 (GraphPad Software, Inc., La Jolla, CA, USA). First, descriptive statistics were computed and normal distribution of quantitative variables were checked using the Shapiro–Wilk test. The majority of the data were normally distributed, and therefore the data are expressed as means ± SD. In part 1, normally distributed quantitative variables were compared between healthy controls (n = 22) and AS patients (n = 22) with independent sample *t* tests with Bonferroni correction. Non-normally distributed data were compared between these two groups by Mann–Whitney *U* test with Bonferroni correction. The χ^2-test was applied for comparisons of qualitative variables (smoking status and medication use) between groups. In part 2, changes in normally distributed quantitative variables were assessed by a paired sample *t* test with Bonferroni correction ($n = 14$). Quantitative variables in time that were changes in non-normally distributed data were analysed by Wilcoxon signed rank tests with the Holm–Bonferroni correction for multiple comparisons. Statistical significance wat set at $P < 0.05$ (2-tailed). An *a priori* sample size calculation was not possible due to a lack of data on this specific topic. However, the observed statistical power was calculated by use of GPower®, and is mentioned in the tables.

3 | RESULTS

3.1 | Subjects' characteristics

No significant differences were found at baseline between healthy controls and AS patients, with the exception of physical activity level and prevalence of type 2 diabetes (Table 1, $P < 0.05$). The following medications were taken before surgery by AS patients *vs.* healthy controls: anticoagulants ($n = 12$ *vs.* $n = 7$), beta-blockers ($n = 3$ *vs.* $n = 1$), anti-hypertensive agents ($n = 12$ *vs.* $n = 9$), anti-arrhythmic agents ($n = 2$ *vs.* $n = 1$), diuretics ($n = 6$ *vs.* $n = 2$), statins ($n = 10$ *vs.* $n = 8$), antibiotics ($n = 1$ *vs.* $n = 1$), analgesic ($n = 1$ *vs.* $n = 1$), anti-inflammatory agents ($n = 1$ *vs.* $n = 1$) and other medications ($n = 9$ *vs.* $n = 6$) that included benzodiazepines, metformin and thyroid hormones.

TABLE 1 Characteristics of healthy controls and AS patients

Characteristic	Healthy controls($n = 22$)	AS patients ($n = 22$)
Male (n)	12	12
Female (n)	10	10
Age (years)	71 ± 9	70 ± 11
Height (m)	1.64 ± 0.09	1.65 ± 0.10
Weight (kg)	71.9 ± 12.6	75.4 ± 12.7
Body mass index (kg m^{-2})	26.7 ± 2.80	27.7 ± 4.10
Systolic blood pressure (mmHg)	138 ± 16	147 ± 20
Diastolic blood pressure (mmHg)	82 ± 9	80 ± 11
Waist circumference (m)	0.95 ± 0.11	0.94 ± 0.17
Habitual physical activity (h $week^{-1}$)	3.2 ± 1.5	**2.4 ± 0.6***
Medication (n)		
Anticoagulants	7	12
Beta-blockers	1	3
Anti-hypertensive agents	9	12
Antiarrhythmic agents	1	2
Diuretics	2	6
Statins	8	10
Antibiotics	1	1
Analgesics	1	1
Anti-inflammatory medications	1	1
Others	6	9
Other cardiovascular disease risk factors		
Type 2 diabetes (taking metformin, n)	0	4
Smoking (n)	2	3

Values are represented as means ± SD except where otherwise stated. Patients taking blood pressure-lowering drugs are considered hypertensive. *Significantly different between groups ($P < 0.05$).

3.2 | Cardiopulmonary and skeletal muscle response to exercise in healthy controls *vs.* pre-operative AS patients

The cycling power output was successfully matched (at 25% of predicted W_{peak}) between healthy controls and AS patients (26 ± 5 *vs.* 26 ± 6 W; $P = 0.88$, Table 2). However, in AS patients RER (0.87 ± 0.10 *vs.* 0.92 ± 0.04), $W/\dot{V}_{O_2}$ (29.9 ± 6.6 *vs.* 35.5 ± 6.5 W ml^{-1} min^{-1}), $\dot{V}_E/\dot{V}_{O_2}$ (25.7 ± 2.9 *vs.* 31.1 ± 4.4) and $\dot{V}_E/\dot{V}_{CO_2}$ (30.6 ± 7.6 *vs.* 34.0 ± 5.3) were significantly elevated and $\dot{V}_{O_2}$ (884 ± 125 *vs.* 736 ± 126 ml min^{-1}) and $\dot{V}_{O_2}$/HR (9.8 ± 2.0 *vs.* 8.5 ± 1.2 ml $beat^{-1}$) were significantly lowered, as compared with healthy controls ($P < 0.05$). In addition, exercise-onset $\dot{V}_{O_2}$ kinetics were significantly slower in AS patients *vs.* healthy controls (i.e. the time constant was 44.5 ± 15.9 *vs.* 33.3 ± 7.6 s, $P < 0.05$). No other significant differences were observed between these groups ($P > 0.05$, Table 2).

3.3 | Peri-operative and early post-operative parameters in AS patients

During mini-AVR the average aortic cross-clamp time was around 37 ± 9 min and patients were connected to the heart lung machine for a total duration of 53 ± 11 min. After mini-AVR, patients stayed at the ICU for an average period of 36 ± 17 h, and were intubated for 6.8 ± 4.1 h. During the first two post-operative days, blood CRP concentrations were significantly elevated ($P < 0.05$). The patients were hospitalized for 7 ± 2 days (Table 3).

During the 21-day follow-up, eight patients were unable to retake the exercise test due to complications, hospitalization and/or the inability to perform the exercise test (excessive dyspnoea $n = 4$,

TABLE 2 Cardiopulmonary exercise test parameters in healthy controls *vs.* AS patients

Parameter	Healthy controls ($n = 22$)	AS patients ($n = 22$)	P
Cycling power output (W)	26 ± 5	26 ± 6	0.848
Respiratory gas exchange ratio	0.87 ± 0.10	0.92 ± 0.04	**0.002**
Lactate (mmol l^{-1})	3.2 ± 0.9	3.1 ± 1.4	0.257
Borg ratings of perceived exertion	9.1 ± 1.5	9.9 ± 2.4	0.392
Heart rate (beats min^{-1})	91 ± 10	87 ± 13	0.481
% predicted heart rate	54 ± 13	57 ± 70	0.275
Oxygen uptake (ml min^{-1})	884 ± 125	736 ± 126	**0.001***
$W/\dot{V}_{O_2}$ (W ml^{-1} min^{-1})	29.9 ± 6.6	35.5 ± 6.5	**0.007***
Carbon dioxide output (ml min^{-1})	772 ± 138	678 ± 129	0.061
O_2 pulse (ml $beat^{-1}$)	9.8 ± 2.0	8.5 ± 1.20	**0.049**
Expiratory volume (l min^{-1})	22.8 ± 4.8	22.6 ± 3.5	0.884
Equivalent for O_2	25.7 ± 2.9	31.1 ± 4.4	**0.002***
Equivalent for CO_2	30.6 ± 7.6	34.0 ± 5.3	**0.004**
Breathing frequency (breaths min^{-1})	20 ± 3	21 ± 5	0.232
Tidal volume (ml)	1186 ± 320	1053 ± 352	0.274
Exercise-onset $\dot{V}_{O_2}$ kinetics			
Tau (s)	33.3 ± 7.6	44.5 ± 15.9	**0.004***
Amplitude (ml)	609 ± 79	414 ± 68	**<0.001***
Total O_2 deficit (l)	6.9 ± 4.2	5.9 ± 6.7	0.195
Resting oxygen uptake (ml min^{-1})	278 ± 73	316 ± 61	**0.024**

Values are represented as means ± SD. *Sufficiently powered ($\alpha \geq 0.80$). The bold indicates a significant difference between groups or during follow-up ($P < 0.05$).

TABLE 3 Peri-operative and early post-operative parameters in AS patients

Parameters	Value
Cardiopulmonary bypass time (min)	53 ± 11
Cross clamp time (min)	37 ± 90
Intubation time (h)	6.8 ± 4.1
Length of stay in intensive care unit (h)	36 ± 17
Bleeding during surgery (ml)	147 ± 215
Bleeding 12 hours post-operative (ml)	190 ± 192
Bleeding 24 hours post-operative (ml)	271 ± 22
C-reactive protein, pre-operative (mg dl^{-1})	2.0 ± 2.2
C-reactive protein, post-operative day 1 (mg dl^{-1})	58 ± 39
C-reactive protein, post-operative day 2 (mg dl^{-1})	207 ± 90
C-reactive protein, post-operative day 3 (mg dl^{-1})	143 ± 80
Hospitalization (days)	7 ± 2

pulmonary embolism $n = 1$, pneumonia $n = 1$, pericarditis $n = 1$, pleural effusion $n = 1$): these patients were not included in the final analysis.

3.4 | Cardiac function before and after mini-AVR

As expected, mini-AVR led to a significant increase in AVA ($P < 0.05$, Table 4). Moreover, this surgical intervention significantly led to increments in E, E/A, DT (only for the first 5 days after surgery) and lateral E'. No other significant changes in echocardiographic parameters were noticed ($P > 0.05$).

3.5 | Changes in cardiopulmonary and skeletal muscle response to exercise in AS patients after mini-AVR

Five days after mini-AVR, Borg RPE (8.7 ± 1.4 *vs.* 11.1 ± 2.1), $\dot{V}_E/\dot{V}_{O_2}$ (29.3 ± 2.6 *vs.* 36.8 ± 7.4) and $\dot{V}_E/\dot{V}_{CO_2}$ (31.6 ± 3.1 *vs.* 40.1 ± 6.5) (Figure 2a), $\dot{V}_E$ (22.7 ± 3.1 *vs.* 27.5 ± 5.0 l min^{-1}) (Figure 2c), BF (21 ± 5 *vs.* 26 ± 5 breaths min^{-1}) were significantly elevated, while tidal volume (V_t; 1226 ± 264 *vs.* 1077 ± 258 ml) (Figure 2d) was significantly lowered ($P < 0.05$, Table 5). Except for Borg RPE and $\dot{V}_E$, these parameters remained altered at 21 days after mini-AVR ($P < 0.05$). When cardiopulmonary response was compared between 5 and 21 days, HR (94 ± 13 *vs.* 82 ± 17 beats min^{-1}), % predicted HR (61 ± 9 *vs.* 54 ± 12 %) and $\dot{V}_E$ (27.5 ± 5.0 *vs.* 22.8 ± 4.7 l min^{-1}) were significantly lowered. In addition, exercise-onset $\dot{V}_{O_2}$ kinetics were significantly slower after 21 days (i.e. time constant from 42.1 ± 15.6 to 49.1 ± 13.3 s; $P < 0.05$, Table 5; Figure 2b) and $W/\dot{V}_{O_2}$ was significantly increased at 21 days after mini-AVR ($P < 0.05$). At day 5 and day 21 post-operative, rest $\dot{V}_{O_2}$ was significantly decreased ($P < 0.05$).

4 | DISCUSSION

In the present study, it was observed that during endurance-type constant-workload exercise AS patients experienced significantly worse ventilatory equivalents ($\dot{V}_E/\dot{V}_{O_2}$: 31.1 ± 4.4 *vs.* 25.7 ± 2.9, $\dot{V}_E/\dot{V}_{CO_2}$: 34.0 ± 5.3 *vs.* 30.6 ± 7.7; $P < 0.05$; Table 2), as well as a lowered oxygen pulse ($\dot{V}_{O_2}$/HR) (8.5 ± 1.2 *vs.* 9.8 ± 2.0 ml $beat^{-1}$; $P < 0.05$; Table 2) and slowed exercise-onset $\dot{V}_{O_2}$ kinetics, compared with healthy controls. After mini-AVR, and despite the restoration of the AVA, the ventilatory equivalents worsened further within the next 5 days, followed by a further slowing of the exercise-onset $\dot{V}_{O_2}$ kinetics after 21 days.

These pre-operative results were to be expected as AS leads to reductions in cardiac stroke volume and cardiac output, thereby leading to a ventilation–perfusion mismatch (Dulgheru et al., 2016). Moreover, the exercise-onset $\dot{V}_{O_2}$ kinetics were significantly slowed in AS patients *vs.* healthy controls (tau: 44.5 ± 15.9 *vs.* 33.3 ± 7.6 s, $P < 0.05$). Assessing exercise-onset $\dot{V}_{O_2}$ kinetics is a sensitive tool for the specific evaluation of oxidative capacity of the skeletal muscles: they are significantly faster in skeletal muscle with predominantly slow-twitch fibres and with increased exercise-induced activation of oxidative muscle enzymes (Hughson, 2009). Moreover, exercise-onset $\dot{V}_{O_2}$ kinetics are significantly slowed in patients with heart disease (Zhang et al., 1993) and they are improved by exercise training intervention (Murias, Kowalchuk, & Paterson, 2010). These findings may point towards dysregulation in oxidative phosphorylation, and

TABLE 4 Echocardiographic analysis of AS patients before and after mini-AVR

	Pre-operative (*n* = 14)	Post-operative day 5(*n* = 14)	*P*-value 1	Post-operative day 21(*n* = 14)	*P*-value 2	*P*-value 3
LVOT (VTI)	24 ± 4	22 ± 5	0.219	22 ± 6	0.311	0.723
E (ms)	80 ± 27	100 ± 24	**0.001***	97 ± 29	**0.034**	0.182
A (ms)	96 ± 26	91 ± 26	0.374	94 ± 30	0.515	0.114
E/A	0.87 ± 0.30	1.11 ± 0.20	**0.022***	1.08 ± 0.30	**0.028**	0.701
DT (ms)	252 ± 70[a]	190 ± 46	**0.010***	196 ± 53	0.170	0.814
A duration (ms)	140 ± 20	143 ± 27	0.769	144 ± 15	0.796	0.610
Septal *E′* (cm s^{-1})	4.5 ± 1.1*	6.1 ± 1.9	0.060	5.8 ± 1.5	0.073	0.890
Lateral *E′* (cm s^{-1})	5.2 ± 1.5*	8.1 ± 2.3	**0.013***	7.8 ± 1.9	**0.046***	0.670
E/E′	16.1 ± 6.4	14.8 ± 5.3	0.395	14.5 ± 6.4	0.533	0.272
EF	66 ± 7	60 ± 10	0.287	60 ± 9	0.082	0.859
SV	85 ± 22	75 ± 21	0.361	79 ± 28	0.227	0.088
SV index	50 ± 11	41 ± 15	0.197	43 ± 13	0.223	0.969
CO	5.5 ± 1.1[a0]	5.7 ± 1.5[C]	0.977	5.3 ± 1.9	0.582	0.136
Cardiac index	3.3 ± 0.5[a0]	3.2 ± 0.8[C]	0.333	2.9 ± 0.8	0.362	0.223
AVA (cm^2)	0.8 ± 0.2	2.0 ± 0.5	**0.000***	2.0 ± 0.5	**0.000***	0.413
PAP (mmHg)	28 ± 13	29 ± 12	0.279	28 ± 13	0.734	0.789

Values are represented as means ± SD. *A*, trans-mitral peak late diastolic velocity; AVA, aortic valve area; CO, cardiac output; DT, deceleration time; *E*, trans-mitral peak early diastolic velocity; *E′*, early diastolic mitral annular velocity); EF, ejection fraction; PAP, pulmonary artery pressure; SV, stroke volume. *Sufficiently powered ($\alpha \geq 0{,}80$). *P*-value 1: between pre-operative and post-operative day 5; *P*-value 2: between pre-operative and post-operative day 21; *P*-value 3: between post-operative day 5 and day 21. The bold indicates a significant difference between groups or during follow-up ($P < 0.05$).

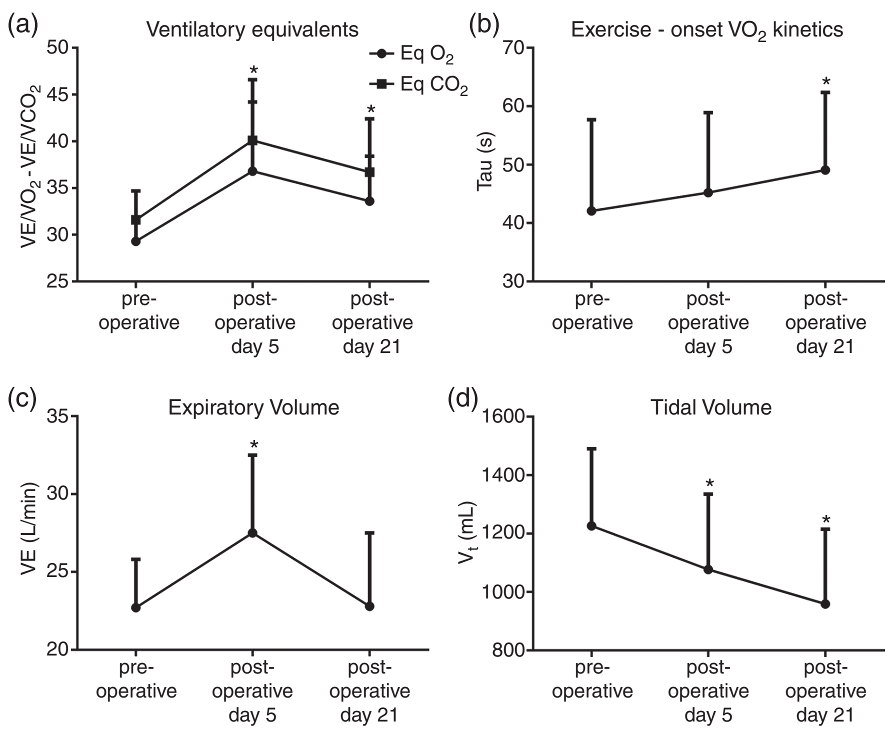

FIGURE 2 Cardiopulmonary exercise test parameters at pre-operative and post-operative days 5 and 21 after mini-AVR. (a) Ventilatory equivalents were significantly elevated at post-operative days 5 and 21. (b) Exercise-onset $\dot{V}_{O_2}$ kinetics were significantly slowed at day 21 after mini-AVR. (c) Expiratory volume was only significantly elevated at day 5 after mini-AVR. (d) Tidal volume was significantly decreased at both post-operative days 5 and 21

TABLE 5 Cardiopulmonary exercise test parameters before and 5 and 21 days after mini-AVR

	Pre-operative ($n = 14$)	Post-operative day 5($n = 14$)	*P*-value 1	Post-operative day 21($n = 14$)	*P*-value 2	*P*-value 3
Respiratory gas exchange ratio	0.92 ± 0.04	0.92 ± 0.05	0.611	0.91 ± 0.05	0.414	0.961
Lactate (mmol l^{-1})	2.9 ± 0.8	3.1 ± 0.8	0.529	2.7 ± 0.8	0.360	0.422
Borg ratings of perceived exertion	8.7 ± 1.4	11.1 ± 2.1	**0.002***	10.5 ± 2.3	0.060	0.505
Heart rate (beats min^{-1})	91 ± 9	94 ± 13	0.465	82 ± 17	0.875	**0.022**
% predicted heart rate	59 ± 7	61 ± 9	0.464	54 ± 12	0.272	**0.022**
Oxygen uptake (ml min^{-1})	777 ± 95	752 ± 88	0.112	678 ± 107	**0.044**	0.071
$W/\dot{V}_{O_2}$ (W ml^{-1} min^{-1})	35.5 ± 6.5	37.3 ± 6.8	0.087	40.2 ± 7.5	**0.041**	0.074
Carbon dioxide output (ml min^{-1})	722 ± 96	692 ± 96	0.179	627 ± 122	0.059	0.136
Oxygen pulse (ml $beat^{-1}$)	8.6 ± 1.2	8.1 ± 0.8	0.156	8.5 ± 1.7	0.742	0.377
Expiratory volume (l min^{-1})	22.7 ± 3.1	27.5 ± 5.0	**0.001***	22.8 ± 4.7	0.658	**0.010**
Equivalent for O_2	29.3 ± 2.6	36.8 ± 7.4	**0.001***	33.6 ± 4.8	**0.003***	0.140
Equivalent for CO_2	31.6 ± 3.1	40.1 ± 6.5	**0.000***	36.7 ± 5.7	**0.002***	0.126
Breathing frequency (breaths min^{-1})	21 ± 5	26 ± 5	**0.000**	25 ± 6	**0.005**	0.053
Tidal volume (ml)	1226 ± 264	1077 ± 258	**0.002**	959 ± 265	**0.003**	0.277
Exercise-onset $\dot{V}_{O_2}$ kinetics						
Tau (s)	42.1 ± 15.6	45.2 ± 13.7	0.483	49.1 ± 13.3	**0.049**	0.371
Amplitude (ml)	419 ± 62	384 ± 71	0.193	391 ± 60	**0.024**	0.771
Total O_2 deficit (l)	6.2 ± 7.0	10.6 ± 6.0	0.064	8.2 ± 7.2	0.382	0.159
Resting oxygen uptake (ml)	321 ± 62	367 ± 57	**0.021**	292 ± 72	0.226	**0.010**

Values are represented as means ± SD. *Sufficiently powered ($\alpha \geq 0.80$). *P*-value 1: between pre-operative and post-operative day 5; *P*-value 2: between pre-operative and post-operative day 21; *P*-value 3: between post-operative day 5 and day 21. The bold indicates a significant difference between groups or during follow-up ($P < 0.05$).

it is hypothesized that such skeletal muscle dysregulation could be attributed to and/or aggravated by physical inactivity (as evidenced by a significantly lowered physical activity in AS patients *vs.* healthy controls (2.4 ± 0.6 *vs.* 3.2 ± 1.5 exercise h $week^{-1}$, Table 1, $P < 0.05$). However, it remained unknown whether the reduced cardiopulmonary and skeletal muscle function during exercise could be restored by mini-AVR, using data from healthy subjects as reference/target values.

As a result of mini-AVR, the AVA increased significantly (from 0.8 ± 0.2 to 2.0 ± 0.5 cm^2, Table 4, $P < 0.05$), together with improvements in cardiac diastolic function (*E/A* from 0.87 ± 0.30 to 1.11 ± 0.20, and lateral E' from 5.2 ± 1.5 to 8.1 ± 2.3 cm s^{-1}, $P < 0.05$, Table 4). As a result, by restoring the aortic valve the rapid-phase (or passive) left-ventricular filling was significantly enhanced. On the other hand, indicators for systolic function (e.g. left ventricular ejection fraction, stroke volume (index) and cardiac output) did not change during early follow-up ($P > 0.05$). Therefore, an enhanced left-ventricular filling does not automatically result in enhanced cardiac output, at least not within a few weeks. According to the findings of Treibel *et al.*, systolic function, after sAVR, is known to improve only after a period of 6 months to 1 year due to the regression of cellular hypotrophy that is accompanied by structural, functional and biomarker improvement (Treibel et al., 2018). Therefore, changes in systolic function after mini-AVR are not likely to be observed this early after surgery in the present study. After sAVR the PAP did not change, which is noteworthy because raised PAPs can increase the ventilatory equivalents for CO_2 during exercise.

Despite the observed improvements in AVA and diastolic function after mini-AVR, and despite the participation in an in-hospital rehabilitation programme, a significantly worsened pulmonary function and gas exchange efficiency during exercise within the 5 days after surgery was identified. The V_t decreased significantly by ~12% while $\dot{V}_E/\dot{V}_{O_2}$ and $\dot{V}_E/\dot{V}_{CO_2}$ increased significantly (both by ~26–27%, Table 5, $P < 0.05$). These data may point towards insufficient inspiratory lung volumes together with worsening of ventilation–perfusion mismatch early after mini-AVR. The underlying mechanisms for this worsening in pulmonary function may be due to chest wall restriction, diffusion impairment and/or decreased diaphragm course (Chetta et al., 2006). Atelectasis and reduced lung volumes due to pain inhibition could also lead to reductions in ventilation in the presence of preserved cardiac output, causing changes in ventilatory equivalents. Such manifestations may then hypothetically lead to shallow breathing (as evidenced by significantly elevated BF) and elevations in Borg RPE and $\dot{V}_E$ (as a compensatory pulmonary response to a limited gas exchange efficiency). These findings are in keeping with previous studies demonstrating that surgical manipulation after cardiothoracic surgery can have a direct impact on the respiratory system leading to pulmonary dysfunction and complications that are known to elevate postoperative morbidity and mortality (Calderon et al., 2009). Minimal sternotomy access or conventional median total sternotomy for replacing the aortic valve has been reported to significantly worsen the pulmonary function (as assessed by a mobile respiratory spirometric device) within the first 7 days following surgery (Calderon et al., 2009). Importantly, 8 out of 22 patients (36%) were unable to re-execute the same exercise test due to complications, mostly pulmonary. It thus appears that the pulmonary system is significantly affected early after mini-AVR. It is of important clinical relevance to determine and further explore the impact of mini-AVR on the pulmonary system and gas exchange physiology. These insights will lead to better post-operative treatment and thus to improved patients' quality of life and functional capacity during post-operative recovery.

Twenty-one days after mini-AVR, the ventilation–perfusion match remained significantly altered during exercise (as evidenced by significant elevations in $\dot{V}_E/\dot{V}_{CO_2}$ and $\dot{V}_E/\dot{V}_{O_2}$, Table 5, $P < 0.05$), but also the exercise-onset $\dot{V}_{O_2}$ kinetics slowed significantly (tau: from 42.1 ± 15.6 to 49.1 ± 13.3 s, Table 5, $P < 0.05$). Besides pulmonary dysfunction, it is also well known that cardiothoracic surgery (e.g. coronary artery bypass graft surgery) leads to an acute catabolic response and skeletal muscle wasting within a few weeks (Hansen et al., 2015). Moreover, critical illness leads to rapid reductions in type 1 and 2 fibre cross-sectional area (Dirks, Hansen, Van Assche, Dendale, & Van Loon, 2015). As a result, such a decrement in type 1 fibre size may be associated with reductions in oxidative capacity. In healthy individuals, a 1 week bed rest leads to significant decrements in mitochondrial respiration capacity (Dirks et al., 2016). When patients were discharged from the hospital, they did not experience relief of pulmonary symptoms (e.g. dyspnoea, pulmonary oedema), which leads to significant exhaustion when performing any small activity of daily living. This resulted in a sedentary lifestyle (based on patient reports) in the first month after mini-AVR. The in-hospital rehabilitation was only delivered for up to 5 days in the present study. These data may indicate that patients who have undergone mini-AVR are in need of a tailored post-operative treatment and improved rehabilitation intervention. More specifically, the pulmonary and skeletal muscular system should be targeted, as soon as possible after mini-AVR, if deemed medically safe. Therefore, the role of early exercise intervention as an additional post-operative treatment can be very important in preventing further decreases in pulmonary function and functional capacity.

Nowadays, cardiac rehabilitation (CR) is a well-established treatment that improves exercise capacity and quality of life, and lowers morbidity/mortality (Piepoli et al., 2014). Current CR guidelines remain, however, to be optimized for patients receiving heart valve surgery due to a lack of data (Piepoli et al., 2014). As a result of a deterioration in pulmonary and skeletal muscle function, a multidisciplinary rehabilitation intervention with endurance exercise training can lead to improvements in quality of life, functional capacity and exercise tolerance after mini-AVR (Ribeiro et al., 2017). However, from our experience, we believe that CR will be more successful if inspiratory muscle training is performed as soon as possible after mini-AVR. Inspiratory muscle training (inspiration against resistance), for example, has been shown to result in fewer post-operative complications, a shorter hospital stay and improved maximum inspiratory pressures when applied immediately after cardiothoracic surgery (Ge, Wang, Hou, Yang, & Fa, 2018). In addition, to preserve skeletal muscle function, sufficiently intense mobilization after mini-AVR is warranted (Ramos Dos Santos, Aquaroni Ricci, Aparecida Bordignon Suster, de Moraes Paisani, & Dias Chiavegato, 2017). In order to accomplish such optimized early post-operative care, a multidisciplinary approach is mandatory.

Due to the observed high drop-out rate, a large proportion of the patients were not able to follow any rehabilitation programme to improve post-operative recovery after mini-AVR surgery. Therefore, standard implementation of prehabilitation before mini-AVR could be considered to improve post-operative recovery and quality of life, especially in frail and older patients. During this prehabilitation period, the focus can be laid on increasing and optimizing mobility, nutrition and respiratory status of the patient (Weinkam, 2017).

This study has some limitations and the data should thus be interpreted in light of these shortcomings. Due to a lack of data on this specific topic, it was not possible to execute a valid *a priori* sample calculation. Therefore, it was decided to recruit as many patients as possible and report the observed statistical power of the executed comparisons. Although the study sample in the cross-sectional study seemed rather low ($n = 22$ in both groups), the observed statistical power seemed sufficient (≥0.80) for most of the observed inter-group differences. However, during follow-up there was a high drop-out due to pulmonary complications, leaving 14 patients to be analysed. Therefore the patients who recovered best from mini-AVR were analysed in this study and thus the impact of mini-AVR on the pulmonary and skeletal muscular system may be even worse. The observed power analysis revealed that for some inter-group comparisons the sample size should have been greater. On the other hand, Bonferroni corrections for multiple comparisons were applied, thus minimizing the risk for a type 1 error. Finally, right-ventricular cardiac function was not evaluated in this study.

In conclusion, despite restoration of the AVA, a decline in pulmonary function emerges during exercise early after mini-AVR, followed by skeletal muscle dysfunction a few weeks later. These data reiterate the need for optimized multidisciplinary post-operative treatment and early rehabilitation to enhance patients' outcomes.

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COMPETING INTERESTS

None declared.

AUTHOR CONTRIBUTIONS

H.B., A.Y., B.R. and D.H. contributed to the conception or design of the work. H.B., A.Y., B.R., K.K., G.C., I.F., P.D., H.V., L.J.C.vL. and D.H. contributed to the acquisition, analysis, or interpretation of data for the work. H.B., A.Y., B.R., K.K., G.C., I.F., P.D., H.V. and D.H. drafted the manuscript. H.B., L.J.C.vL. and D.H. critically revised the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

ORCID

Dominique Hansen https://orcid.org/0000-0003-3074-2737

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