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Does an undetected obstructive sleep apnea influence the natural course and success of cardiac rehabilitation after cardiac surgery?

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ABSTRACT

BACKGROUND: Obstructive Sleep Apnea (OSA) is common in patients with cardiovascular diseases (CVD) and can negatively impact the course of CVD. However, scarce data are available for patients before or after cardiac surgery (CS) in the context of OSA.

AIM: This study investigated the impact of an undetected OSA on the results of cardiac rehabilitation (CR) in patients after CS.

DESIGN: Observational study over a period of 3 months following CS

SETTING: Inpatient CR after CS or cardiac interventions

POPULATION: CS cohort referred to a CR program to an inpatient rehabilitation clinic in Switzerland.
METHODS: In this prospective observational study 256 patients were screened for OSA at the entry of CR via a level III screening device (ApneaLink Air^{TM}). They were stratified into two groups: Apnea Hypopnea Index (AHI) $\geq$15 or <15/h. A comprehensive assessment was performed at entry and end of CR including six-minute walk test (6-MWT), Functional Independence Measure (FIM), Hospital Anxiety and Depression Scale, MacNewHeart (MNH), STOP-BANG Questionnaire (SBQ) and Epworth Sleepiness Scale (ESS).
All patients participated in a comprehensive CR program with a mean duration of approximately 3 weeks. Another OSA screening was performed at the end of the PR program and after 3 months in order to observe the clinical course of OSA.
RESULTS: An AHI $\geq$15/h was found in 133 patients (59%) at baseline, 54% after 3 weeks and 43% after 3 months. The AHI $\geq$15/h-group was older, had a higher BMI, more frequent hypertension and coronary artery disease, and higher ESS and SBQ scores compared to the AHI <15/h-group. The results of the STOP-BANG and ESS questionnaires showed a statistically significant but weak positive correlation with AHI. However, in both groups ESS did not improve from baseline to the end of CR. A multivariable logistic regression model confirmed age and ESS as independent positive predictors of OSA. No differences were found between both groups according to the results of the 6-MWT, HADS, MNH.
CONCLUSIONS: OSA had a high prevalence in a large CS cohort referred to CR. However, moderate-severe OSA, though symptomatic, had no significant influence on the outcome during CR and on the parameters representing success.
CLINICAL REHABILITATION IMPACT: In our study the improvements during CR after CS were not influenced by the presence of significant OSA which is remarkable since the presence of OSA is thought to be associated with increased rates of cardiovascular adverse events after cardiovascular intervention or CS. This is true at least for the success of CR after CS. The long-term consequences of untreated OSA in CVD remain unclear and are still the subject of current research.

Key words: Obstructive sleep apnea, cardiac surgery, cardiac rehabilitation, six-minute walk test, Mac New Heart, Functional Independence Measure

Introduction

Sleep disordered breathing, obstructive sleep apnea (OSA) in particular, is a very common disorder of repetitive pharyngeal collapse during sleep leading to oxygen desaturation and hypercapnia followed by sleep fragmentation, which contribute to cardiovascular, metabolic, and neurocognitive consequences. OSA is highly prevalent in patients with established cardiovascular disease.[1] Previous studies reported that the prevalence of OSA -defined as more than 5 apneas or hypopnoeas per h (AHI≥5) of sleep plus excessive daytime sleepiness- affects 17% of men and 9% of women aged between 50 and 70 years.[2]

OSA is debated to be associated with higher risks of vascular death, myocardial infarction, stroke, heart failure and arrhythmia especially in patients with concomitant arterial hypertension. This is commonly attributed to oxyhaemoglobin desaturation and surges of sympathetic activity.[3, 4] In addition, OSA is may be associated with an increase systemic inflammation, endothelial dysfunction and platelet aggregation, which also contribute to adverse vascular events. Continuous positive airway pressure (CPAP) is known to be the effective standard therapy of OSA. However, several studies published in the last 5 years found no consistent effects on the prevention of cardiovascular disease (CVD) events in OSA when treated with CPAP and in consequence the role of OSA as a contributor to CVD is still discussed.[4-7]

In a recent published large multicenter study preoperative OSA screening with polygraphy was performed in patients at high cardiovascular risk undergoing major visceral or vascular surgery or orthopedic surgery. Patients with OSA (AHI ≥ 30/h) had a significantly increased risk (adjusted HR; 2.23 [95 %CI, 1.49-3.34]; P = 0.001) for postoperative cardiovascular events (myocardial damage, heart failure, thromboembolic event, atrial fibrillation, stroke or

death) within 30 days. But mild or moderate sleep apnea showed no significant risk increase.[8] Limited data are available for patients before or after cardiac surgery. One small study investigated 40 patients scheduled for coronary artery bypass graft surgery (CABG) and 41 patients scheduled for general surgery with overnight polysomnography.[9] 50.2% of CABG patients had a preoperative AHI of ≥15/h. Another study found significant desaturations of ≥5/h in 64% and ≥15/h in 29.2% of 89 patients two weeks after cardiac surgery.[10]

Several recent studies, meta-analyses and recommendations of national and international guidelines suggest a beneficial effect of cardiac rehabilitation (CR) in patients with coronary artery disease and other cardiac conditions especially being associated with reduced mortality after an acute coronary event.[11] Exercise training is a cornerstone in CR leading to reductions in cardiovascular (CV) event rates, hospitalisations, and improves CVD risk profile, exercise capacity, muscle strength and endurance, quality of life and life expectancy in patients with CVD (risk).[12] Since OSA contributes to decreased energy levels and motivation throughout the day and insufficient motivation is commonly reported as a cause of reduced participation in exercise programs, the presence of OSA in CR might have a negative impact on the therapeutic success of this intervention.[13, 14]

Overall, OSA is highly prevalent in cardiac patients, either before or after cardiac surgery. To our knowledge, no data exist about the natural course of OSA during the first 3 months after cardiac surgery and its influence on functional improvement during cardiac rehabilitation. Therefore, we aimed to i) estimate the prevalence of sleep apnea after cardiac surgery and ii) compare results of CR inter- and intraindividually between patients with and without OSA.

Materials and methods

Study design and study population

This study was a single-center prospective observational study including patients referred to cardiac rehabilitation (CR) after cardiac surgery at the Zuercher RehaZentren Klinik Wald, Switzerland. After completion of informed consent, clinical parameters, laboratory data, demographic data, different questionnaires, medical history and physical examination were assessed. Screening for OSA was performed with the ApneaLink Air^{TM} device (ResMed GmbH, Switzerland) during their second night at CR (visit 1) and repeated after 20 days (visit 2) on average before patients finished CR. Another assessment was performed after 3 months (visit 3) at home, where the device was sent by mail and was returned the next day by mail. The German versions were used for all provided questionnaires. The Epworth Sleepiness Scale (ESS) and STOP-BANG questionnaire (SBQ) were completed by the participants at visits 1 and 2 as well as the Six-Minute Walk Test (6-MWT). After the first screening for sleep apnea with the ApneaLink Air^{TM} we divided the group into patients with an AHI < 15/h and $\geq$ 15/h and compared them to the results in 6-MWT, Functional Independence Measure (FIM), Hospital Anxiety and Depression Scale (HADS), SBQ, ESS, MacNewHeart Questionnaire (MNH), and the impact of heart surgery on OSA. A composite endpoint of events at 3 months (cardiovascular death, non-fatal myocardial infarction, non-fatal cardiac arrest, revascularisation procedure, new atrial fibrillation and stroke) was assessed by phone call. The project was started after full approval from the ethics committee (Swissethics KEK-ZH-No. 2015-0548) and was registered at the Clinical Trials Registry (NCT02632162).

In- and exclusion criteria

Subjects, who fulfilled the following criteria were included into this project: Written informed consent after participants` information; at least 18 years of age. Only patients after cardiac surgery referred for CR were included. Exclusion criteria were age < 18 years of age and already known or treated sleep apnea.

Components of cardiac rehabilitation

Components of CR in Switzerland are defined by the Swiss Working Group for Cardiovascular Prevention, Rehabilitation and Sports Cardiology (www.SCPRS.ch). Inpatient CR is a standardized intensive short-term program, lasting approximately 3 weeks, starts immediately after hospital discharge and includes a defined number of exercise sessions, psychological, dietary and smoking counselling. According to the SCPRS standards and recommendations, all CR provides a multidisciplinary rehabilitation team on board, providing exercise training and disease specific information and education.

Assessments

The ApneaLink Air™ is a Level III portable device that recorded up to five signals for diagnostic purposes: Breathing effort, pulse, oxygen saturation, nasal airflow and snoring. It provided reliable information, was a simple, easy-to-use device, and was highly sensitive and specific in calculating AHI, when compared with the AHI obtained from full polysomnography (PSG).[15] The validation study showed a sensitivity for the ApneaLink™ greater than 80% at all AHI values, achieving the predefined endpoint criterion. The ApneaLink™ device had the highest sensitivity and specificity at an AHI value of 15 or more events per hour (91% and 95%, respectively). It also showed high sensitivity and

specificity (> 80%) at AHI values of 10 or more events per hour and 20 or more events per hour.

In the current study an AHI of ≥ 15/h was assumed to represent an at least moderate OSA with a possible impact on cardiovascular events and outcome.

The SBQ is a clinically useful tool with high sensitivity that can be used to screen patients for moderate and severe OSA recording Snoring, Tiredness, Observed Apnea, (Blood-) Pressure, BMI > 35, Age > 50, Neck (> 43cm), and Gender.[16] The SBQ was originally developed to stratify post-operative complication risk related to OSAS in a group of adult patients before a major surgery. A recent meta-analysis proved that SBQ is a superior tool for detecting mild, moderate, and severe OSAS compared to other questionnaires but the clinical merit was affected by the population on which it was tested.[17] The sensitivity for the STOP-Bang score ≥3 as the cut-off to predict any OSA (apnea hypopnea index (AHI) >5), moderate-to-severe OSA (AHI >15) and severe OSA (AHI >30) is 83.9%, 92.9% and 100% respectively.[16]

The ESS is a method for measuring daytime sleepiness by using a very short questionnaire. It is a self-administered questionnaire with 8 questions. Patients are asked to rate their usual chances of dozing off or falling asleep while engaged in eight different activities on a 4-point scale (0-3). The reference range of 'normal' ESS scores is zero to 10. That is the same as the range defined by the 2.5 and 97.5 percentiles. ESS scores of 11-24 represent increasing levels of 'excessive daytime sleepiness' (EDS). The method is frequently used in sleep medicine for the diagnosis of sleep disorders and as an endpoint in intervention trials of patients with obstructive sleep apnea syndrome.[18] It is estimated that the minimum clinically important improvement of the ESS lies between −2 and −3.[19]

A standardized 6-min walk test (6-MWT) was performed twice (one at the beginning and one at the end of CR) according to the American Thoracic Society guidelines.[20] The minimal clinically important difference of the 6-MWT is discussed to be between 30-45 meters in cardiac patients receiving a medical intervention.[21] An increase in walking distance in the 6-MWT of 45 meters in the pre/post comparison is accepted as a successful response to the training intervention during CR. We suspected a lower increase in walking distance in the OSA (AHI $\geq$ 15/h) group due to lower vigilance and motivation to participate in regular training.

The MNH Questionnaire claims to objectively, reliably and validly record the impairments of quality of life caused by cardiovascular diseases from the subjective viewpoint of the patient. It belongs to the disease-specific quality of life instruments. Following the WHO definition of "health", this questionnaire is divided into three areas: physical, emotional and social health-related quality of life.[22] With the instrument FIM™ (Functional Independence Measure) functional limitations of patients are measured by 18 characteristics. A uniform scale with 7 values is used for all characteristics.[23] In this study experienced rehabilitation personnel conducted the FIM assessments. Hospital Anxiety and Depression Scale (HADS) - was used to measure anxiety and depression in patients with physical illness or (possibly psychogenic) physical complaints.[24]

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) and categorical variables as number and percentages. Pairwise comparison across groups was performed using the Wilcoxon rank-sum test for continuous variables, and the chi squared test or

categorical variables. In case of five or less observations in a particular category we used the Fischer's Exact test for categorical variables. We further investigated the correlation between results of the STOP-Bang questionnaire with AHI at baseline by calculating Spearman's rank-order correlation coefficient with the corresponding p-value. We then used univariable and multivariable logistic regression to test the association of potential predictor variables with presence of OSA at baseline (AHI <15/h: no relevant sleep apnea; AHI ≥15/h: sleep apnea present). All variables with a p-value of ≤ 0.1 from the univariable model were included in a multivariable model. The final full model was then defined using a stepwise backwards selection process based on the Akaike information criterion (AIC). Statistical significance was accepted at $p<0.05$. We used the statistical software packages R version 3.6.2 and R-Studio Version 1.2.5033.

Results

Data of 226 patients were collected at visit 1. At visit 2 a complete data set of 146 patients was collected. At visit 3 the results of the ApneaLink Air™ of 132 patients could be measured. Overall, the most frequent surgical intervention performed before CR was coronary artery bypass surgery (CABG, n=139, 61,5%) and valve replacement (n=51, 22,6%), followed by mitral valve reconstruction (n=22, 9,7%) and transcatheter aortic valve implantation (TAVI, n=21, 9,3%) (Table I). Seventeen participants had combined interventions (CABG+valve) and one participant had three interventions before CR. Patients with an AHI ≥ 15/h were older, had a higher body weight and BMI. Further, we observed a higher frequency of coronary artery disease and hypertension. Left ventricular ejection fraction (LVEF) was comparable in both groups. Mean LVEF was normal (55.9% and 55.6%) and LVEF <50% was present in 14.3% and 11.3% (Table I).

OSA parameters

At visit 1 OSA with an AHI ≥ 15/h was found in 59% of the patients (n=133). At the end of CR (visit 2) an AHI ≥ 15/h was found in 79 patients (54%) and at visit 3 in 57 patients (43%), representing a moderate but significantly reduction of OSA over the observation period of 3 months.

Overall, AHI was 24.71/h ± 19.75 at visit 1, 24.21/h ± 20.03 (p=0.811 vs baseline) at visit 2 and 17.89/h ± 15.20 at visit 3 (p<0.001 vs. baseline). AHI values of patients with AHI of <15/h at baseline did not differ at visit 2 and 3 compared to baseline (Figure 1). However, AHI of patients with moderate to severe sleep apnea at baseline decreased from 36.28/h ± 17.93 to 30.57/h ± 14.89 at 3 months, p=0.024.

Questionnaires and Assessments

60 (29,7%) patients had a SBQ score < 3 points, 147 (70,3%) ≥ 3 (Figure II). Patients with an AHI ≥ 15/h had higher scores in the ESS and STOP-BANG questionnaire (Table I). Anxiety or depression, as measured in the HADS questionnaire, was rare in both groups without differences between both groups. FIM values and health-related quality of life measured by the MNH questionnaire were not different in the intergroup comparison. The improvements achieved at the end of CR were significant as shown in the intragroup comparison. In the intergroup comparison improvements regarding the emotional and social domain of the MNH questionnaire were significantly larger in patients with an AHI ≥ 15/h than in those with an AHI <15/h. (Table II).

The results of the STOP-BANG and ESS questionnaires showed a statistically significant but weak positive correlation with AHI (Figures 3a and 3b).

6-MWT responder vs non-responder

We further divided the cohort into responders (≥45 meters) and non-responders (<45 meters) to CR according to the increase in the walking distance measured in 6-MWT at baseline and at the end of CR. Eighty-eight percent of the participants increased their walking distance ≥ 45 meters. Except for higher age and more TAVI procedures in the non-responder group, no significant differences in the OSA parameters, ESS, STOP-BANG, FIM, MNH, and HADS (all Table III).

Adverse events

At 3 months no cardiovascular adverse events were reported in the whole study group.

Regression analysis

In the univariable analysis age (per 10 years) (odds ratio (OR) 1.45, 95% confidence interval (CI) 1.15-1.83), BMI (OR 1.07, CI 1.01-1.13), history of coronary artery disease (OR 1.94, CI 1.10-3.41) and ESS score (OR 1.11, CI 1.10-1.20) showed a positive association with the outcome sleep apnea (AHI ≥15/h), while increasing GFR values (OR 0.99, CI 0.97-0.99) were negatively associated with the outcome (Table IV). In the multivariable model only age, BMI and ESS scores were positively associated with presence of sleep apnea, with similar effect sizes and significance levels as in the univariable analysis (Table IV).

Discussion

To the best of our knowledge this is the first study showing that moderate-to-severe OSA with a mean AHI of 36/h had no influence on CR outcome in a lager cohort after cardiac surgery although significant OSA was found in almost 60% of mostly symptomatic patients.

Prevalence of OSA

The prevalence of OSA in cardiovascular patients is known to be high as also confirmed by the results of this study. Indeed, in coronary artery disease (CAD) patients 6 months after revascularization an AHI ≥15/h was present in 64% of 662 patients.[25] In contrast, a recent study in 1152 CR patients found clinically significant sleep apnea (AHI ≥15/h) in 33% of patients with a mean AHI of 14 ± 16/h (range 0-106/h).[26] While the OSA rate and AHI values remained unchanged after 3 weeks, we found a significant reduction of OSA and AHI values in the OSA group after three months. One reason might be the reduction of fluid accumulation in the tissue, also in the larynx area, which is often observed in the early period after cardiac surgery. Another reason could be the positive impact of exercise based rehabilitation. Indeed, supervised exercise training in patients with OSA was found to reduce sleep apnea and to improve cardiorespiratory fitness, daytime sleepiness, and sleep efficiency.[27]

Predictors for OSA

We performed a univariable regression analysis and found several parameters being associated with OSA, such as age, BMI, coronary artery disease and ESS questionnaire. In the multivariable analysis only age (per 10 years), coronary artery disease and ESS remained predictive.

Age is an already known risk factor for OSA and is positive associated with daytime sleepiness.[28, 29] However, it remains unclear, if cardiovascular risk is associated with age in patients with OSA. Indeed, several studies have shown an attenuation rather than an increase of cardiovascular risk with higher age.[30] Interestingly, if severe symptoms of daytime sleepiness are present, an association between OSA and mortality might be present in elderly patients >65 years of age.[31]

With respect to CAD, it has been shown, that patients with severe OSA have significantly more fatal and non-fatal cardiac events. However, controversy exist how relevant the high prevalence of OSA is and how beneficial CPAP therapy might be. Recent clinical trials of CPAP treatment showed neutral results regarding cardiovascular endpoints.[4, 6] The consensus appears to be that patients with more severe OSA, generally pure OSA will benefit with regard to combined CVD-related outcomes linearly with increasing hours of CPAP use, e.g. to improve blood pressure and quality of life.

Is OSA relevant for functional improvement and outcome after cardiac surgery?

There is limited evidence, that untreated OSA in cardiovascular patients can have negative impact on postoperative recovery, reduced quality of life and worse outcome during cardiac rehabilitation.[32, 33] We used 6-MWT and different assessments to investigate the impact of OSA after cardiac surgery. All patients improved significantly in 6-MWT, FIM, MNH and HADS, we did not observe any impact of AHI $\geq$15 /h in any of the assessments.

In an additional analysis we divided the cohort into responders ($\geq$45 meters) and non-responders (<45 meters) during CR. However, there were no differences between both groups except for higher age and more TAVI procedures in the non-responder group.

In our study the FIM was used to assess a patient's level of disability at baseline as well as improvements during CR. Admission FIM scores are important predictors for the clinical course and discharge outcomes of CR patients, with those with higher admission FIM scores having a shorter length of stay and greater likelihood of discharge to home. The admission FIM scores can help to establish realistic goals.[34] In our study the improvement of the FIM Score was not influenced by the presence of significant OSA which is remarkable and corroborates the missing impact of moderate to severe OSA on improvements in the 6-

MWT. In addition, we observed significant higher ESS values in the OSA group, which is thought to negatively impact physical activity.[13, 14]

Presence of OSA is thought to be associated with increased rates of cardiovascular adverse events after cardiovascular intervention or cardiovascular surgery.[35] A recent meta-analysis of 9 cohort and case-control studies reported an increased risk for postoperative cardiovascular complications in patients with OSA also after major non-cardiac surgery.[36] However, we did not find any major adverse events after 3 months in our cohort.
Finally, although OSA did not affect the performance increase in this cohort, screening for OSA after cardiac surgery seems to be indicated in view of the high prevalence during CR with 54% of all patients at the end of CR. Higher STOP Bang values correlate with higher AHI values and could help to identify OSA if pulsoxymetry or polysomnography is not available.

Limitations

This study has some limitations that should be mentioned. At first this a single center study representing a cohort of the greater Zurich area. Generalizing results to other populations should therefore be done with caution. Second, although the ApneaLink Air™ device is validated, it cannot replace a polysomnography (PSG) as the gold-standard for detection of OSA. But performing PSG in over 200 participants could not be realized in this setting. Third, between visit 1 and 3 we registered a significant loss of evaluable data, which might lead to an overestimation of the AHI during the course of the study. However, this study was conducted to detect the impact of OSA on the results of CR as a primary endpoint.

Conclusions

We found a high prevalence of OSA in patients referred to CR after cardiac surgery, in particular compared to healthy persons. Moderate-severe OSA in these patients was symptomatic and associated with more daytime sleepiness. However, moderate-severe OSA did not have any influence on the results and success of CR.

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NOTES

Conflict of interest. —The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript

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Authors contributions. —MH and AT contributed to the concept of the work, designed this study and the data collection instruments. SP collected data. MS, MSch and MH carried out the initial analyses and interpretation of data, drafted the initial manuscript. All authors critically reviewed and revised the manuscript for important intellectual content and approve the final manuscript as submitted and agree to be accountable for all aspects of the work.

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TABLES

Table I.— *Baseline characteristics of the participants with an AHI <15/h and ≥15/h.*

	Total cohort (N=226)	**AHI<15 (N=93)**	**AHI≥15 (N=133)**	**p value**
Days between surgery and inclusion to study, mean (SD)	11.8 (4.6)	12.5 (4.9)	11.3 (4.4)	0.079
Age, mean (SD)	66.5 (12.1)	63.5 (12.6)	68.7 (11.2)	0.001
Sex, male	167 (73.9%)	64 (68.8%)	103 (77.4%)	0.146
Height, mean (SD)	170.5 (8.7)	171.1 (9.4)	170.2 (8.3)	0.460
Body weight, mean (SD)	78.7 (15.7)	76.6 (15.8)	80.1 (15.6)	0.036
BMI, mean (SD)	27.0 (4.8)	26.2 (4.9)	27.6 (4.6)	0.007
Surgical intervention				
Valve replacement surgery	51 (22.6%)	26 (28.0%)	25 (18.8%)	0.105
CABG	139 (61.5%)	52 (55.9%)	87 (65.4%)	0.149
TAVI	21 (9.3%)	6 (6.5%)	15 (11.3%)	0.252
MIDCAP	1 (0.4%)	0 (0.0%)	1 (0.8%)	1.000[1]
Mitral valve reconstruction	22 (9.7%)	10 (10.8%)	12 (9.0%)	0.666
MitraClip	1 (0.4%)	1 (1.1%)	0 (0.0%)	0.412[1]
Aortic dissection repair	10 (4.4%)	5 (5.4%)	5 (3.8%)	0.744[1]
Comorbidities				
Coronary artery disease	153 (67.7%)	55 (59.1%)	98 (73.7%)	0.021
Hypertension	156 (69.0%)	56 (60.2%)	100 (75.2%)	0.017
Atrial fibrillation	56 (24.8%)	22 (23.7%)	34 (25.6%)	0.744
Type 2 diabetes	45 (19.9%)	13 (14.0%)	32 (24.1%)	0.062

Dyslipidemia	166 (73.5%)	66 (71.0%)	100 (75.2%)	0.480
Peripheral artery disease	22 (9.7%)	7 (7.5%)	15 (11.3%)	0.349
Stroke	4 (1.8%)	0 (0.0%)	4 (3.0%)	0.090[1]
Current smoker	25 (11.1%)	14 (15.1%)	11 (8.3%)	0.110
COPD	12 (5.3%)	7 (7.5%)	5 (3.8%)	0.241
ICD/CRT-D	3 (1.3%)	1 (1.1%)	2 (1.6%)	[2]
LVEF, mean (SD)	55.7 (9.9)	55.9 (10.3)	55.6 (9.6)	0.474
Normal	189 (84.4%)	76 (83.5%)	113 (85.0%)	0.708
LVEF <50	28 (12.5%)	13 (14.3%)	15 (11.3%)	
LVEF <30	7 (3.1%)	2 (2.2%)	5 (3.8%)	
NYHA class				0.349[1]
I	59 (26.1%)	28 (30.1%)	31 (23.3%)	
II	166 (73.5%)	65 (69.9%)	101 (75.9%)	
III/IV	1 (0.4%)	0 (0.0%)	1 (0.8%)	
Questionnaires and assessments				
6-MWT	302.0 (116.7)	319.7 (115.8)	290.5 (116.1)	0.077
ESS score	6.5 (4.1)	5.6 (3.5)	7.1 (4.3)	0.015
STOP-Bang	3.4 (1.5)	3.1 (1.5)	3.6 (1.5)	0.036
MacNewHeart - Emotional	76.8 (13.6)	76.3 (13.7)	77.1 (13.6)	0.769
MacNewHeart - Physical	60.5 (13.3)	60.3 (13.7)	60.7 (13.1)	0.938
MacNewHeart - Social	68.1 (14.2)	69.2 (14.5)	67.3 (14.1)	0.296
FIM total	109.3 (8.9)	109.9 (10.2)	108.9 (7.9)	0.265
FIM practical-motoric	77.6 (6.6)	78.5 (6.8)	77.0 (6.3)	0.092
FIM socio-cognitive	31.7 (3.3)	31.4 (4.3)	31.9 (2.4)	0.502
HADS A	3.7 (3.1)	4.1 (3.5)	3.4 (2.9)	0.307
HADS D	4.6 (3.5)	4.8 (3.6)	4.4 (3.4)	0.479

BMI, Body-Mass-Index; CABG, Coronary artery bypass grafting; TAVI, transcatheter aortic valve implantation; MIDCAB, minimal invasive direct coronary artery bypass surgery; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; LA, left atrium; COPD, Chronic Obstructive Pulmonary Disease; ECG, Electro Cardio Gram; STOP-BANG, STOP-BANG questionnaire; NYHA, New York Heart Association; HADS, Hospital Anxiety and Depression Scale; A, Anxiety; D, Depression; ESS, The Epworth Sleepiness Scale; 6-MWT, Six-Minute Walk Test; FIM, Functional Independence Measure; MNH, MacNewHeart Questionnaire; AHI, Apopnea-Hypopnea-Index; AI, Apnea-Index; HI, Hypopnea-Index; SO2, Saturation for Oxygen; CS, Cheyne-Stones breathing; ODI, Oxygen Desaturation Index
[1]Fishers exact test was used instead of chi squared tests as one or more categories contained five or less observations; [2] No statistical test performed due to small numbers

Table II.—*Change in questionnaires and functional assessment scores from baseline to the end of CR (3 weeks) by AHI at baseline.*

	AHI<15/h		**AHI≥15/h**		
Assessment	**Difference**	**P[1]**	**Difference**	**P[1]**	**P[2]**
6-MWT	159.2 (89.3)	< 0.001	150.3 (88.9)	< 0.001	0.342
ESS	-0.4 (3.6)	0.335	-1.3 (4.6)	0.119	0.567
STOP-Bang	-0.4 (1.2)	0.023	-0.4 (1.1)	0.980	0.505
FIM overall	10.8 (8.2)	< 0.001	11.2 (6.6)	< 0.001	0.314
FIM practical-motoric	8.5 (5.8)	< 0.001	9.5 (5.3)	< 0.001	0.148
FIM socio-cognitive	-1.3 (2.9)	< 0.001	1.7 (2.9)	< 0.001	0.790
HADS A	-1.3 (2.9)	< 0.001	-1.5 (2.4)	0.005	0.642
HADS D	-1.2 (2.8)	< 0.001	-1.4 (2.6)	0.062	0.755
MacNewHeart – Emotional	9.5 (12.5)	< 0.001	13.2 (11.0)	< 0.001	0.047
MacNewHeart – Physical	7.8 (11.1)	< 0.001	9.9 (10.2)	< 0.001	0.354
MacNewHeart – Social	7.6 (14.1)	< 0.001	13.8 (11.7)	< 0.001	0.005

STOP-BANG, STOP-BANG questionnaire; HADS, Hospital Anxiety and Depression Scale; A, Anxiety; D, Depression; ESS, The Epworth Sleepiness Scale; 6-MWT, Six-Minute Walk Test; FIM, Functional Independence Measure; MNH, MacNewHeart Questionnaire; AHI, Apopnea-Hypopnea-Index; [1] p for intragroup difference in means (baseline vs. 3 weeks); [2] p for intergroup difference (AHI<15/h vs. AHI≥15/h)

Table III.— *Baseline characteristics of responders (increase in the walking distance measured in 6-MWT ≥ 45 meters) and non-Responder (< 45 meters).*

	<45m (N=23)	**≥45m (N=172)**	**p value**
Days between surgery and inclusion to study	11.5 (4.3)	11.5 (4.2)	0.960
Age	72.4 (10.9)	65.4 (12.0)	0.008
Sex - male	15 (65.2%)	128 (74.4%)	0.349
Height	168.3 (12.8)	170.9 (8.1)	0.662
Body weight	73.7 (17.2)	79.8 (15.3)	0.053
BMI	26.0 (5.3)	27.2 (4.7)	0.129
Surgical intervention			
Valve replacement surgery	4 (17.4%)	41 (23.8%)	0.605
CABG	12 (52.2%)	111 (64.5%)	0.249
TAVI	5 (21.7%)	10 (5.8%)	0.020[1]
Mitral valve reconstruction	2 (8.7%)	18 (10.5%)	1.000[1]
MitraClip	0 (0.0%)	1 (0.6%)	1.000[1]
Aortic dissection	1 (4.3%)	6 (3.5%)	0.591[1]
OSA related items			
AHI	23.1 (21.1)	25.2 (19.9)	0.367
ODI	32.8 (24.1)	33.4 (20.6)	0.661
Mean sO2	90.6 (2.5)	90.9 (2.3)	0.912
Minimum sO2	78.9 (7.9)	78.9 (7.3)	0.673
Basal sO2	93.4 (3.2)	93.5 (2.5)	0.655
Assessments			
STOP-Bang questionnaire	2.9 (1.4)	3.5 (1.6)	0.101
ESS score	6.0 (3.7)	6.6 (4.1)	0.619

MacNewHeart - Emotional	76.7 (13.8)	76.7 (13.3)	0.940
MacNewHeart - Physical	63.1 (15.1)	60.1 (13.0)	0.254
MacNewHeart - Social	69.9 (16.2)	67.7 (14.1)	0.482
HADS A	4.4 (3.1)	3.6 (3.2)	0.240
HADS D	3.7 (3.5)	4.6 (3.4)	0.221
FIM overall	108.1 (9.4)	110.0 (8.9)	0.161
FIM practical-motoric	77.1 (7.1)	78.1 (6.5)	0.247
FIM socio-cognitive	31.0 (2.8)	31.9 (3.4)	0.069

BMI, Body-Mass-Index; CABG, Coronary artery bypass grafting; TAVI, transcatheter aortic valve implantation; MIDCAB, minimal invasive direct coronary artery bypass surgery; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; LA, left atrium; COPD, Chronic Obstructive Pulmonary Disease; ECG, Electro Cardio Gram; STOP-BANG, STOP-BANG questionnaire; NYHA, New York Heart Association; HADS, Hospital Anxiety and Depression Scale; A, Anxiety; D, Depression; ESS, The Epworth Sleepiness Scale; 6-MWT, Six-Minute Walk Test; FIM, Functional Independence Measure; MNH, MacNewHeart Questionnaire; AHI, Apopnea-Hypopnea-Index; AI, Apnea Index; HI, Hypopnea-Index; SO2, Saturation for Oxygen; CS, Cheyne-Stones breathing; ODI, Oxygen Desaturation Index

1Fishers exact test was used instead of chi squared tests as one or more categories contained five or less observations

Table IV. — *Uni- and multivariable logistic regression analysis to test the association of potential predictors for the presence of sleep apnea (AHI≥15/h) at baseline.*

	Univariable analysis			Multivariable analysis		
Variable	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Sex (for females)	0.64	0.35-1.17	0.148	--	--	--
Age at baseline (per 10 years)	1.45	1.15-1.83	0.002	1.49	1.15-1.93	0.003
BMI (kg/m^2)	1.07	1.01-1.13	0.030	--	--	--
Coronary artery disease	1.94	1.10-3.41	0.022	1.77	0.95-3.30	0.075
Type 2 diabetes	1.95	0.96-3.96	0.065	--	--	--
COPD	0.48	0.15-1.57	0.228	--	--	--
Lipid metabolism diseases	1.24	0.68-2.25	0.480	--	--	--
Smoking status	0.51	0.22-1.18	0.114	--	--	--
NYHA			0.267	--	--	--
II	1.40	0.77-2.55		--	--	--
III/IV	NA	NA		--	--	--
LVEF (%)	1.00	0.97-1.03	0.865	--	--	--
ECG (baseline sinus rhythm)			0.854	--	--	--
Atrial fibrillation	0.91	0.35-2.41		--	--	--
Pacing	5.11	0.62-42.35	0.130	--	--	--
Intervention (baseline surgery)	1.56	0.61-4.00	0.353	--	--	--
No sternotomy (baseline sternotomy)	1.04	0.52-2.05	0.922	--	--	--
GFR (ml/min)	0.99	0.97-1.00	0.033	--	--	--
Hemoglobin (g/L)	1.00	0.98-1.02	0.945	--	--	--
Creatinine (mmol/L)	1.01	1.00-1.02	0.112	--	--	--
ESS questionnaire	1.11	1.03-1.19	0.008	1.12	1.03-1.21	0.005

BMI, Body-Mass-Index; LVEF, left ventricular ejection fraction; LA, left atrium; COPD, Chronic Obstructive Pulmonary Disease; ECG, Electro Cardio Gram; NYHA, New York Heart Association; ESS, The Epworth Sleepiness Scale; AHI, Apnea-Hypopnea-Index; GFR, glomerular filtration rate; OR, odds ratio; CI, confidence interval

TITLES OF FIGURES

Figure 1.— The Apnea–Hypopnea Index (AHI) at baseline, 3 weeks and 3 months stratified by baseline AHI values.

Figure 2.— Results of the STOP-BANG Questionnaire (SBQ) in relation to the Apnea-Hypopnea-Index (AHI) at baseline

Figure 3a. — Correlation between results of the STOP-BANG questionnaire and the Apnea–Hypopnea Index (AHI) at baseline

Figure 3b. — Correlation between results of the Epworth Sleepiness Scale (ESS) questionnaire and the Apnea-Hypopnea-Index (AHI) at baseline