ERJ Express. **Published on March 22, 2012 as doi: 10.1183/09031936.00172211**

Natural course of sleep-disordered breathing after acute myocardial infarction

Stefan Buchner, MD[1]*, Tanja Greimel[1]*; Andrea Hetzenecker, MD[2]; Andreas Luchner, MD[1]; Okka W. Hamer, MD[3]; Kurt Debl, MD[1]; Florian Poschenrieder, MD[3]; Claudia Fellner, PhD[3]; Günter A. J. Riegger, MD[1]; MS; Michael Pfeifer, MD[1, 2]; Michael Arzt, MD[1]

*Authors contributed equally

Affiliations

[1] Klinik und Poliklinik für Innere Medizin II, Universitätsklinikum Regensburg, Germany

[2] Pneumologie, Donaustauf, Germany

[3] Institut für Röntgendiagnostik, Universitätsklinikum Regensburg, Germany

Corresponding Author: Michael Arzt, MD, Center for Sleep Medicine, Department of Internal Medicine II, University Hospital Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany

Phone: +49 (941) 944 7281, Fax: +49 (941) 944 7282.

e-mail: michael.arzt@klinik.uni-regensburg.de

Research supporting funding:

Michael Arzt has received unrestricted grant support from Resmed (Martinsried, Germany), Philips Home Healthcare Solutions (Murrysville, PA, USA), and the German Foundation for Cardiac Research (Deutsche Stiftung für Herzforschung).

Word count text: 2,949 (Introduction to Discussion < 3,500)

Copyright 2012 by the European Respiratory Society.

ABSTRACT

The aim of this study was to test whether an improvement of left ventricular ejection fraction in the early phase after acute myocardial infarction is associated with a reduction of the severity of central and obstructive sleep apnea.

Forty consecutive patients with acute myocardial infarction underwent polysomnography and cardiovascular magnetic resonance imaging within 5 days and 12 weeks after the event to assess sleep apnea and cardiac function. We stratified the sample in patients who improved their left ventricular ejection fraction (EF) within 12 weeks by ≥5% (improved-EF-group, ΔEF 9±1% , n=16) and in those who did not (unchanged-EF-group, ΔEF -1±1%, n=24).

Prevalence of sleep apnea (≥15 apneas and hypopneas/h) within ≤5 days after myocardial infarction was 55%. Apneas and hypopneas/h were significantly more reduced in the improved-EF-group compared to the unchanged-EF-group (-10±3 versus 1±3/h, p=0.036). This reduction was based on a significant alleviation of obstructive events (-7±2 versus 4±3/h, p=0.009), while the reduction of central events was similar between groups (p=0.906).

An improvement of cardiac function early after myocardial infarction is associated with an alleviation of sleep apnea. This finding suggests that reevaluation of treatment indication for sleep apnea is needed, when a change in cardiac function occurs.

Wordcount Abstract: 199

Key words: heart failure, ventilation, coronary artery disease, acute myocardial infarction, sleep apnea

Obstructive and central sleep apnea (OSA and CSA) is highly prevalent in patients with chronic heart failure [1-3], as well as in patients with acute left ventricular failure, e.g. acute myocardial infarction (AMI) [4-6]. The interactions between sleep apnea and heart failure (HF) are bi-directional: 1) Sleep apnea may contribute to the progression of HF by exposing the heart to intermittent hypoxia, increased preload and afterload, sympathetic activation and vascular endothelial dysfunction. For example in a previous observational study the presence of sleep apnea early after AMI was linked to impaired recovery of cardiac function [6]. Ultimately, both obstructive and central SA confer an increased mortality risk in patients with chronic HF [7-9]. 2) Conversely, there is epidemiological [10] and clinical evidence that cardiovascular disease and especially HF can contribute to the development or worsening of sleep apnea. It has been clearly demonstrated for several treatments of HF that improvement of cardiac function can alleviate or even abolish CSA. Examples for treatments improving cardiac function in patients with CSA include mitral valvuloplasty [11, 12], implantation of a biventricular cardiac device [13, 14] and cardiac transplantation [15]. However, the effect of an improvement of cardiac function on the severity of OSA has not been studied yet.

There is evidence from physiological experiments that fluid overload in HF with consecutive nocturnal rostral fluid shift is associated with upper airway narrowing [16] and the severity of OSA [17, 18].This fluid shift was directly related to the degree of leg edema and sitting time and inversely related to the degree of physical activity [17].This mechanism may be reversed or attenuated by an improvement of cardiac function followed by less leg edema and rostral fluid shift.

Thus we hypothesized, that an increase in ejection fraction (EF) in the early phase after AMI is associated with a reduction of the severity of CSA as well as OSA. To test this hypothesis we studied a sample of patients with AMI and successful percutaneous coronary intervention (PCI). In this context the acute AMI is a model for acute heart failure with one group of patients who improve their cardiac function and others whose left ventricular function remains impaired in

the early phase after AMI, when treated according to current international guidelines for therapy of AMI [19].

METHODS

Patients

In a prospective observational clinical study, patients with an AMI, who were referred to the Universitätsklinikum Regensburg, Germany, between 03/2009 and 05/2010 were evaluated for eligibility (figure 1). Inclusion criteria were 1) age between 18 and 80 years, 2) primary AMI with ST elevation in ECG, 3) successful PCI within 24 hours after AMI and 4) written informed consent. Medications were given according to international guidelines [19].

Exclusion criteria were 1) age under 18 or over 80 years, 2) former AMI with Q-waves in the ECG, 3) indication for a second PCI or surgical myocardial revascularization, 4) cardiac shock (need of catecholamines), 5) implanted cardiac device or other contraindications for cardiovascular magnetic resonance imaging (CMR), 6) known treated or untreated sleep apnea or at least moderate degree of lung diseases and 7) former stroke. The protocol was approved by the local ethics committee and all patients provided written informed consent. Eligible patients underwent an overnight in-laboratory sleep study (polysomnography, PSG) and CMR ≤5 days and 12 weeks after PCI.

Patients were stratified according to the change of left ventricular ejection fraction (ΔEF= EF at 12 weeks – EF baseline): 1) the sample of patients who improved their EF within 12 weeks after AMI by ≥5% (improved EF group and 2) those who did not (ΔEF<5%= unchanged EF group; figure 1). An increase of EF by ≥5% is a strong predictor of survival in heart failure patients [20].

Polysomnography

PSG was performed in all subjects using standard polysomnographic techniques (Alice System, Respironics, Pittsburgh, USA) (8). Respiratory efforts were measured with the use of respiratory inductance plethysmography, and airflow by nasal pressure. Sleep stages, arousals as well as apneas and hypopneas and respiratory effort-related Arousals (RERA) were determined according to AASM by one experienced sleep technician blinded to the clinical data [21]. Hypopnea definition A was used [21]. In addition, hypopneas were classified as obstructive if there was out-of-phase motion of the rib cage and abdomen, or if airflow limitation was present. In order to achieve optimal distinction between obstructive and central hypopneas without using an esophageal balloon we used additional criteria such as flattening, snoring, paradoxical effort movements, arousal position relative to hypopneas and associated sleep stage (REM/NREM) [22]. CSA was defined as >50% central apneas and hypopneas of all apneas and hypopneas.

Cardiovascular magnetic resonance

CMR studies were performed on a clinical 1.5 Tesla scanner (Avanto, Siemens Healthcare Sector, Erlangen, Germany), using a phased array receiver coil during breath-hold and ECG triggered. Examination of ventricular function was performed by acquisition of steady-state free precession cine images in standard short axis planes (SSFP, trueFISP; slice thickness 8 mm; inter-slice gap 2 mm; repetition time 60.06 ms; echo time 1.16 ms; flip angle 60°; matrix size 134x192; readout pixel bandwidth 930 Hz/pixel). The number of Fourier lines per heart beat was adjusted to allow the acquisition of 25 cardiac phases covering systole and diastole within a cardiac cycle. The field of view was 300 mm on average and adapted to the size of the patient. Calculation of left ventricular volumes and ejection fraction was performed in the serial short axis slices using commercially available software (syngo Argus, version B15; Siemens Healthcare Sector, Erlangen, Germany).

Statistical analysis

Continuous data are expressed as means ± standard deviation (SD), unless otherwise indicated. Differences between groups were assessed by two-sided *t*-tests for continuous variables and by chi-square tests for nominal variables. If the expected counts were <5, Fisher exact test was used. For comparing changes of outcome variables over time between groups analysis of covariance (ANCOVA) was used. A two sided p-value of <0.05 was considered as statistically significant. All analyses were performed using SPSS 18.0 (SPSS Inc.).

RESULTS

Patient characteristics

Fifty consecutive patients who were admitted to our institution with ST elevation AMI and underwent PCI within the first 24 hours fulfilled the in- and exclusion criteria and gave written informed consent (figure 1). Ten of these patients were excluded from analysis due to withdrawal of informed consent, missing PSG or CMR data. None of the participants died or was lost to follow-up (figure 1). The reminder 40 ~~Such~~ patients were stratified in the improved EF group (n=16) and the unchanged EF group (n=24, figure 1). The improved EF group showed a significant improvement of EF by 9±1%, whereas the unchanged EF group remained unchanged (-1±1%, p<0.001; figure 2). Compared to the patients in the improved EF group, the patients in the unchanged EF group showed no significant differences in age, sex, body mass index, weight or smoking status at baseline (table 1). Furthermore maximum creatine kinase, systolic and diastolic blood pressure, heart rate, kreatinin and EF at baseline were similar in both groups. Both groups showed no significant differences in pre-existing diseases, as diabetes, hypertension or coronary artery disease (table 1). N-terminal pro brain natriuretic peptide (NT-pro BNP) one day after the AMI was similarly elevated in the improved EF and the unchanged EF group, respectively (table 1), indicating a moderate degree of heart failure [23, 24]. Early after PCI the majority of patients had

chest x-ray`s and echocardiograms, that were not part of the study protocol, that indicated pulmonary congestion in 45% and a dilated vena cava inferior without respiratory variation 43%, respectively. The frequency of such signs of pulmonary congestion were similar in both groups (p=0.524 and p=0.728, respectively)

The mean Epworth Sleepiness Scale score at baseline was similar and in the normal range in both groups (p=0.529, table 1), indicating no excessive daytime sleepiness. There were no significant differences in the frequencies of beta-blocker, angiotensin converting enzyme inhibitors/ AT1 antagonists and diuretic use at baseline and at follow up time between the improved and unchanged EF groups (table 2).

Type and severity of sleep apnea in the early phase after AMI

The prevalence of moderate to severe sleep apnea (apnea-hypopnea index, AHI≥15/h) in the entire sample of AMI patients was 55% at <5 days after PCI, of whom half had predominantly CSA and half predominant OSA, respectively. After the 12 weeks observational period there was a modest statistically not significant reduction of sleep apnea prevalence from 55% to 45% (p=0.371).

To evaluate the change of SA severity according to change in EF, we retrospectively stratified in individuals, who improved their EF (improved EF group) and in those who did not (unchanged EF group, figure 1). While the severity of sleep apnea did not change significantly from <5 days to 12 weeks after PCI in the unchanged EF group (AHI: 22±5 to 23±5 per hour, p=0.756), AHI was significantly reduced in the improved EF group (21±4 to 11±2 per hour, p=0.010; figure 3). With respect to sleep apnea type, the improved EF group showed a greater reduction of obstructive AHI compared to the unchanged EF group (p=0.009, table 3, figure 3). In contrast, there was a modest non-significant decrease of central AHI that was similar in the improved EF and unchanged EF groups (p=0.906, table 3, figure 3), which was paralleled by a similar rise of the awake arterialized capillary PCO_2 (table 3, p=0.958, figure 4).

Such findings are confirmed in linear regression models using the changes of LVEF and AHI, central AHI and obstructive AHI within the 12 weeks follow-up period as continuous variables. An increase of LVEF was significantly associated with a decrease of AHI and obstructive AHI but not central AHI (beta-coeficient [95% confidence interval]: AHI, 0.37 [0.17 to 1.69], p=0.018; obstructive AHI 0.33 [0.01 to 1.25], p=0.045; central AHI, 0.14 [-0.35 to 0.95], p=0.339).

While the prevalence of moderate to severe SA (AHI≥15/h) was reduced from 69 to 38% (p=0.077) in the improved EF group at baseline and at follow up, EF unchanged group´s prevalence of moderate to severe SA remained similar (46 to 50%, p=0.773). The prevalence of OSA was in improved EF group (31 to 6%, p=0.070), whereas it showed an increase in unchanged EF group from baseline to follow up time (25 to 31%, p=0.608). In contrast to the EF unchanged group, 31% of the patients from the EF improved group shift from a moderate to severe degree of sleep apnea to less than 15 apneas and hyperpneas per hour of sleep (0 versus 31%, p=0.007). The observed alleviation of sleep apnea in the improved EF group was associated with a significant increase of SaO_2 mean, but SaO_2 min, sleep efficiency, the proportion of N3 and REM sleep stage did not change significantly (table 3).

Clinical course

To evaluate whether cardiac medication or fluid retention had an impact on the association between change of cardiac function and severity of sleep apnea we compared 1) intake of cardiac medication at baseline and follow up (table 1) and 2) the weight change, as a surrogate for fluid retention, over the follow-up period between the improved EF and the unchanged EF groups: 1) patients of both the improved EF and the unchanged EF group showed no significant differences in medication at baseline and follow up (table 1): 1) all patients received acetylsalicyl acid and either clopidogrel or prasugrel for platelet aggregation inhibition and ACE-inhibitors or AT1-antagonists at

baseline. The majority of patients from both groups received betareceptor blockers, only one patient in unchanged EF group did not receive a betareceptor blocker at baseline, because of bradycardia. The vast majority of patients kept the ACE-inhibitors or AT1-antagonists and betareceptor blockers till follow up (table 2). All patients with clinical evidence of fluid overload (e.g. pulmonary or peripheral edema) received diuretics. The use of loop diuretics and thiazid diuretics was similar in both groups at baseline and follow up (table 2). 2) While the improved EF group showed a weight loss, the unchanged EF group gained weight (-1±1 kg versus 2±1 kg, p=0.062).

DISCUSSION

This study provides several novel observations: First, patients ~~within~~ 12 weeks after an AMI have a very high prevalence of moderate to severe sleep apnea (45%), of which approximately 50% is obstructive and 50% is central in nature. Second, there is a modest reduction of sleep apnea prevalence 12 weeks after a first AMI. Third, improvement of cardiac function within the first 12 weeks after AMI is associated with a significant alleviation of sleep apnea severity. In particular, especially obstructive apneas and hypopneas were reduced.

The prevalence of sleep apnea in the acute phase after first AMI in the current study is confirmed by several previous studies [5, 6, 25-27]. Nakashima et al [6] and Yumino et al [25] performed their sleep studies between 14-21 days after primary PCI, whereas other previous studies used a similar time point to assess sleep apnea as the present study at baseline (<5 days after AMI) [5, 26, 28].

In the present study the prevalence of an at least moderate degree of OSA and CSA was 28% and 28% within the first 5 days after AMI, respectively. In none of the patients sleep apnea was suspected on clinical grounds, although 55% of patients had an at least moderate degree of sleep apnea. One reason could be that patients after AMI did not report daytime hypersomnolence. This finding is in accordance to previous reports demonstrating a dissociation of sleep apnea from hypersomnolence in patients with cardiovascular disease such as heart failure and stroke [29-31] . Furthermore in the present study both groups have poor sleep efficiency similar to previous studies of patients with chronic heart failure [30].

Only in one previous report [32] studying sleep apnea early after acute coronary syndrome PSG was used and authors made the distinction between obstructive and central apneas during sleep [21]. Similar to our data moderate to severe OSA and CSA was prevalent in 45% and 37% of acute coronary syndrome patients[32]. However, the reported sample had less impaired cardiac function[32]. In contrast to our data Nakashima and collegues [6] report a proportion of 43% OSA and no CSA in a sample of patients with AMI 14-21 days after the event. In this study cardiac function was similarly impaired as in our patients [6].

A significant proportion of CSA as observed in the present study and the report from Takama et al [32] is plausible in a sample of AMI and acute coronary syndrome patients with a moderate degree of heart failure. In our sample left ventricular function was impaired (EF 44%). Thus the prevalence of CSA and OSA in the AMI patients of our study are comparable to that reported in samples of patients with chronic HF with a similar degree of cardiac impairment [1, 3]. In such samples of chronic HF CSA as well as OSA are associated with impaired prognosis [8, 9].

None of the previous studies focused on the time course of sleep apnea after first AMI [6, 25, 27, 32, 33]. For the first time, we could demonstrate a 18% reduction of apneas and hypopneas per hour of sleep from less than 5 days to 12 weeks after an AMI in association with an improvement of cardiac function. The magnitude of this effect is of clinical relevance in the group of patients, who improve their cardiac function, because 31% of such patients shift from a moderate to severe degree of sleep apnea to mild or no sleep apnea (AHI<15). While many experts would recommend treatment in patients with moderate to severe SDBregardless of symptoms based on the potential effects on cardiovascular outcome, treatment is not indicated~~i~~ in those with mild SDB (AHI<15) without sleep apnea-related symptoms [34]. Considering the high likelihood, that the severity of sleep apnea changes in association with changes of cardiac function, present data support the reevaluation of sleep apnea after improvement of cardiac function in order to prevent unjustified long-term treatment of patients without sleep apnea or mild sleep apnea without sleep

apnea-related symptoms. This finding is in line with previous studies that demonstrated that improvement of cardiac function by various therapies such as implantation of a biventricular cardiac device [13, 14] and cardiac transplantation [15] correlates with an attenuation of the severity of sleep apnea [11-15, 35]. In contrast to most of such studies [11-15] who studied patients with CSA and observed an improvement of CSA, we demonstrated that in our sample of AMI patients the reduction of sleep apnea in the group with an improvement of left ventricular function is mainly caused by the reduction of OSA. There was a modest non-significant reduction of central respiratory events that was similar in patients with improved and unchanged cardiac function, respectively. This finding may be explained by the fact that the awake arterialized capillary PCO_2 similarly increased in both groups within the 12 week follow-up period suggesting an increase in ventilator control stability [36].

Garrigue and collegues [35] observed a reduction of obstructive respiratory events as a consequence of increasing cardiac output by atrial overdrive pacing in patients with bradyarrythmias. However, this was not confirmed in a similar randomized controlled trial [37]. Thus, the current study complements previous reports by demonstrating, that an improvement of cardiac function is also leading to a decrease of OSA´s severity. We assume that the improvement of OSA in patients after AMI, who improved cardiac function, correlates with 1) a decrease of hypervolemia after the acute heart failure and 2) a reduction of ventilator control stability [38]. The observed loss of weight in the group of AMI patients who improved their left ventricular function compared to those with stable ventricular function indicates that such patients reduced their fluid overload. Since neither ventilator control stability nor neck circumference or edema in the neck were assessed, the present study design does not allow firm conclusions with respect to the underlying pathomechanisms for the reduction of obstructive respiratory events in conjunction with an improvement of cardiac function.

Findings have to be interpreted in the light of the following limitations: 1) The finding, that the improved EF group lost more weight than the unchanged EF group, would be in line with the potential pathomechanism that those patients who improved their EF may have less rostral fluidshift contributing to upper airway narrowing [16] and the severity of OSA [17, 18]. Other assessments to support this or other pathomechanisms (e.g. neck circumference and fluid displacement from the legs) were not performed. 2) In addition to cardiac function other factors may have contributed to alleviation of OSA in the improved EF group. Our data support that such effect was not related to time spent in supine position and to changes in medication. 3) Breathing effort can be most accurately measured using an esophageal balloon [21], which was not used in the present study. In spite of the implementation of additional criteria such as flattening, snoring, paradoxical effort movements, arousal position relative to hypopneas and associated sleep stage (REM/NREM) to distinguish between obstructive and central respiratory events [22], some misclassification may have biased the results with respect to the type of sleep apnea.

In summary we showed that moderate to severe sleep apnea is present in 55% of patients in the early phase after AMI and that the number of patients with moderate to severe sleep apnea is reduced by 18% after 12 weeks. Of those patients, who improve their cardiac function within the first 12 weeks after AMI, a substantial proportion (31%) shifts from moderate to severe sleep apnea to no or mild sleep apnea (AHI <15/h) with no or uncertain indication for treatment [34]. In particular, obstructive apneas and hypopneas were reduced.

Thus, the present findings in patients in the early phase after AMI contribute to the clinically important information that the severity of sleep apnea, including OSA, changes when an improvement in cardiac function occurs. Similar effects may be observed after several other medical or surgical interventions in patients with heart failure that improve cardiac function [11-15]. To prevent unjustified long-term treatment in patients with heart failure the present findings

support that the indication for treatment of sleep apnea should be reevaluated, when an improvement in cardiac function occurs.

ACKNOWLEDGEMENT

The authors thank Kerstin Reiter, Daniela Spanja, Heike Koitsch, Astrid Brandl-Novak, Astrid Braune, Ruth Luigart and Katja Ziczinski for excellent technical assistance.

REFERENCES

1. Oldenburg O, Lamp B, Faber L, et al. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. *Eur J Heart Fail.* Mar 2007;9(3):251-257.

2. Schulz R, Blau A, Borgel J, et al. Sleep apnoea in heart failure. *Eur Respir J.* Jun 2007;29(6):1201-1205.

3. Sin DD, Fitzgerald F, Parker JD, et al. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. *Am J Respir Crit Care Med.* Oct 1999;160(4):1101-1106.

4. Hung J, Whitford EG, Parsons RW, Hillman DR. Association of sleep apnoea with myocardial infarction in men. *Lancet.* Aug 4 1990;336(8710):261-264.

5. Lee CH, Khoo SM, Tai BC, et al. Obstructive sleep apnea in patients admitted for acute myocardial infarction. Prevalence, predictors, and effect on microvascular perfusion. *Chest.* Jun 2009;135(6):1488-1495.

6. Nakashima H, Katayama T, Takagi C, et al. Obstructive sleep apnoea inhibits the recovery of left ventricular function in patients with acute myocardial infarction. *Eur Heart J.* Oct 2006;27(19):2317-2322.

7. Corra U, Pistono M, Mezzani A, et al. Sleep and exertional periodic breathing in chronic heart failure: prognostic importance and interdependence. *Circulation.* Jan 3 2006;113(1):44-50.

8. Jilek C, Krenn M, Sebah D, et al. Prognostic impact of sleep disordered breathing and its treatment in heart failure: an observational study. *Eur J Heart Fail.* Jan 2010;13(1):68-75.

9. Wang H, Parker JD, Newton GE, et al. Influence of obstructive sleep apnea on mortality in patients with heart failure. *J Am Coll Cardiol.* Apr 17 2007;49(15):1625-1631.

10. Chami HA, Resnick HE, Quan SF, Gottlieb DJ. Association of incident cardiovascular disease with progression of sleep-disordered breathing. *Circulation.* Mar 29 2011;123(12):1280-1286.

11. Rubin AE, Gottlieb SH, Gold AR, Schwartz AR, Smith PL. Elimination of central sleep apnoea by mitral valvuloplasty: the role of feedback delay in periodic breathing. *Thorax.* Feb 2004;59(2):174-176.

12. Yasuma F, Hayashi H, Noda S, et al. A case of mitral regurgitation whose nocturnal periodic breathing was improved after mitral valve replacement. *Jpn Heart J.* Mar 1995;36(2):267-272.

13. Sinha AM, Skobel EC, Breithardt OA, et al. Cardiac resynchronization therapy improves central sleep apnea and Cheyne-Stokes respiration in patients with chronic heart failure. *J Am Coll Cardiol.* Jul 7 2004;44(1):68-71.

14. Vazir A, Hastings PC, Morrell MJ, et al. Resolution of central sleep apnoea following implantation of a left ventricular assist device. *Int J Cardiol.* Feb 4 2010;138(3):317-319.

15. Mansfield DR, Solin P, Roebuck T, et al. The effect of successful heart transplant treatment of heart failure on central sleep apnea. *Chest.* Nov 2003;124(5):1675-1681.

16. Chiu KL, Ryan CM, Shiota S, et al. Fluid shift by lower body positive pressure increases pharyngeal resistance in healthy subjects. *Am J Respir Crit Care Med.* Dec 15 2006;174(12):1378-1383.

17. Yumino D, Redolfi S, Ruttanaumpawan P, et al. Nocturnal rostral fluid shift: a unifying concept for the pathogenesis of obstructive and central sleep apnea in men with heart failure. *Circulation.* Apr 13 2010;121(14):1598-1605.

18. Redolfi S, Yumino D, Ruttanaumpawan P, et al. Relationship between overnight rostral fluid shift and Obstructive Sleep Apnea in nonobese men. *Am J Respir Crit Care Med.* Feb 1 2009;179(3):241-246.

19. Van de Werf F, Bax J, Betriu A, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J.* Dec 2008;29(23):2909-2945.

20. Cintron G, Johnson G, Francis G, Cobb F, Cohn JN. Prognostic significance of serial changes in left ventricular ejection fraction in patients with congestive heart failure. The V-HeFT VA Cooperative Studies Group. *Circulation.* Jun 1993;87(6 Suppl):VI17-23.

21. Iber C, American Academy of Sleep Medicine. *The AASM manual for the scoring of sleep and associated events : rules, terminology and technical specifications*. Westchester, IL: American Academy of Sleep Medicine; 2007.

22. Randerath W. MC, Oltmann A., Piegnitz C., Treml M., Anudleit N. Evaluation of a new PSG based algorithm to differentiate obstructive and central hypopneas. *Abstract for ERS Congress Barcelona, Thematic poster session P4407.* 2010 2010.

23. Luchner A, Hengstenberg C, Lowel H, et al. NT-ProBNP in outpatients after myocardial infarction: interaction between symptoms and left ventricular function and optimized cut-points. *J Card Fail.* Jun 2005;11(5 Suppl):S21-27.

24. Buchner S, Debl K, Barlage S, et al. Dynamic changes in N-terminal pro-brain natriuretic peptide in acute coronary syndromes treated with percutaneous coronary intervention: a marker of ischemic burden, reperfusion and outcome. *Clin Chem Lab Med.* Jun 2010;48(6):875-881.

25. Yumino D, Tsurumi Y, Takagi A, Suzuki K, Kasanuki H. Impact of obstructive sleep apnea on clinical and angiographic outcomes following percutaneous coronary intervention in patients with acute coronary syndrome. *Am J Cardiol.* Jan 1 2007;99(1):26-30.

26. Mehra R, Principe-Rodriguez K, Kirchner HL, Strohl KP. Sleep apnea in acute coronary syndrome: high prevalence but low impact on 6-month outcome. *Sleep Med.* Sep 2006;7(6):521-528.

27. Meng S, Fang L, Wang CQ, et al. Impact of obstructive sleep apnoea on clinical characteristics and outcomes in patients with acute coronary syndrome following percutaneous coronary intervention. *J Int Med Res.* Sep-Oct 2009;37(5):1343-1353.

28. Marin JM, Carrizo SJ, Kogan I. Obstructive sleep apnea and acute myocardial infarction: clinical implications of the association. *Sleep.* Dec 15 1998;21(8):809-815.

29. Arzt M, Harth M, Luchner A, et al. Enhanced ventilatory response to exercise in patients with chronic heart failure and central sleep apnea. *Circulation.* Apr 22 2003;107(15):1998-2003.

30. Arzt M, Young T, Finn L, et al. Sleepiness and sleep in patients with both systolic heart failure and obstructive sleep apnea. *Arch Intern Med.* Sep 18 2006;166(16):1716-1722.

31. Arzt M, Young T, Peppard PE, et al. Dissociation of obstructive sleep apnea from hypersomnolence and obesity in patients with stroke. *Stroke.* Mar 2010;41(3):e129-134.

32. Takama N, Kurabayashi M. Possibility of close relationship between sleep disorder breathing and acute coronary syndrome. *J Cardiol.* Apr 2007;49(4):171-177.

33. Saito T, Yoshikawa T, Sakamoto Y, et al. Sleep apnea in patients with acute myocardial infarction. *Crit Care Med.* Jul 1991;19(7):938-941.

34. DGSM. S3-Leitlinie, Nicht erholsamer Schlaf, Schlafstörungen. *Somnology.* 2009;13:4-160.

35. Garrigue S, Bordier P, Jais P, et al. Benefit of atrial pacing in sleep apnea syndrome. *N Engl J Med.* Feb 7 2002;346(6):404-412.

36. Naughton M, Benard D, Tam A, Rutherford R, Bradley TD. Role of hyperventilation in the pathogenesis of central sleep apneas in patients with congestive heart failure. *Am Rev Respir Dis.* Aug 1993;148(2):330-338.

37. Pepin JL, Defaye P, Garrigue S, Poezevara Y, Levy P. Overdrive atrial pacing does not improve obstructive sleep apnoea syndrome. *Eur Respir J.* Feb 2005;25(2):343-347.

38. Jordan AS, Wellman A, Edwards JK, et al. Respiratory control stability and upper airway collapsibility in men and women with obstructive sleep apnea. *J Appl Physiol.* Nov 2005;99(5):2020-2027.

FIGURE LEGENDS

Figure 1. Flow diagram of patients. Abbreviations: AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; CMR = Cardiovascular magnetic resonance; PSG = Polysomnography; Improved EF group = improvement of left ventricular ejection fraction within 12 weeks after AMI by ≥5%; Unchanged EF group = improvement of left ventricular ejection fraction within 12 weeks after AMI by <5%

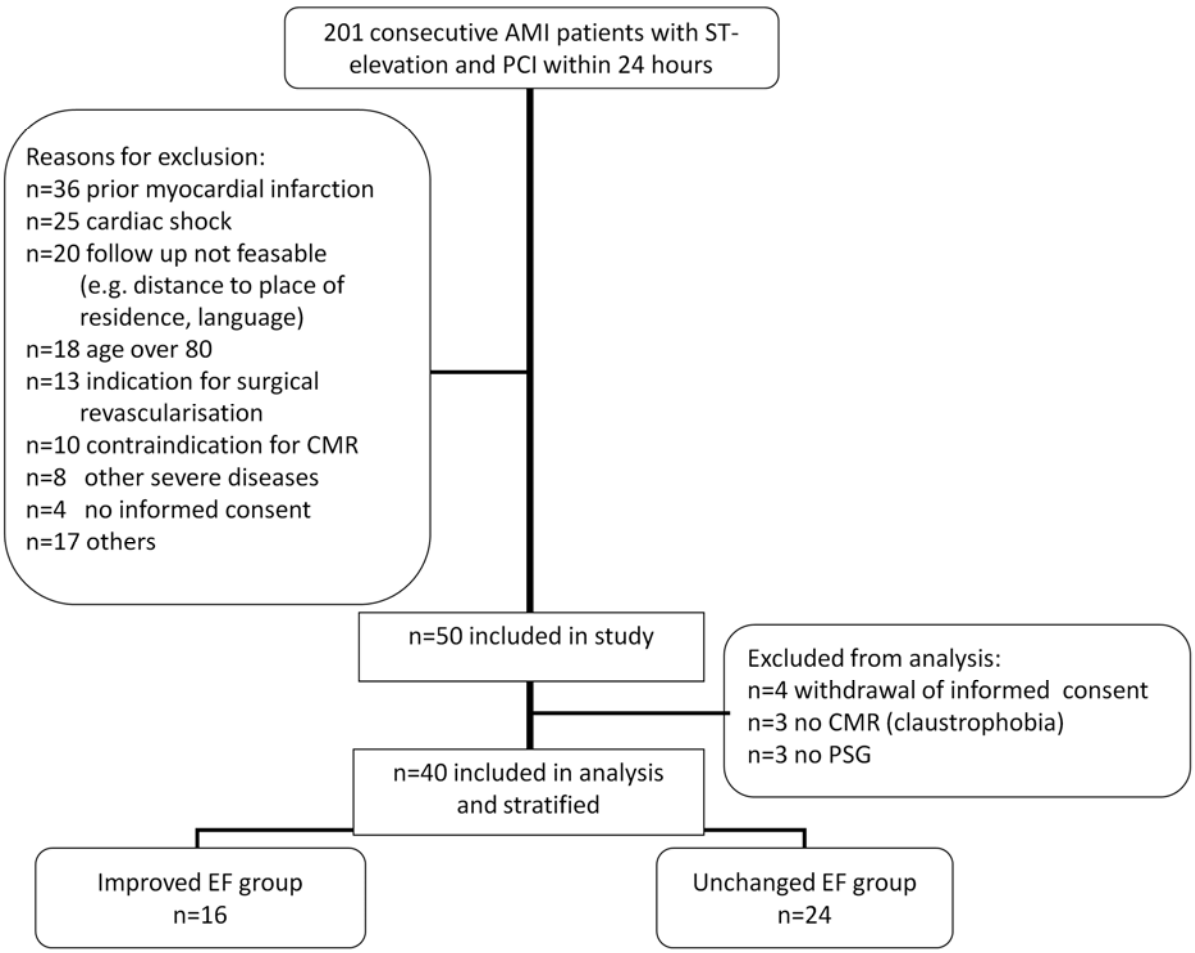

Figure 2. Change of left ventricular ejection fraction. Abbreviations: improved EF group = improvement of left ventricular ejection fraction within 12 weeks after AMI by ≥5%; unchanged EF group = improvement of left ventricular ejection fraction within 12 weeks after AMI by <5%

Figure 2

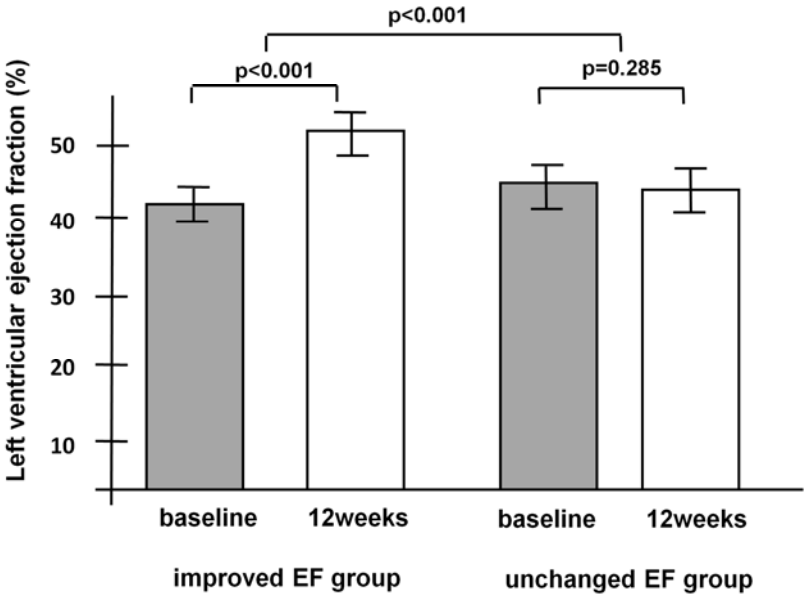

Figure 3. Change of the severity of sleep apnea according to the change of cardiac function. Abbreviations: improved EF group = improvement of left ventricular ejection fraction within 12

weeks after AMI by ≥5%; unchanged EF group = improvement of left ventricular ejection fraction within 12 weeks after AMI by <5%

Figure 3

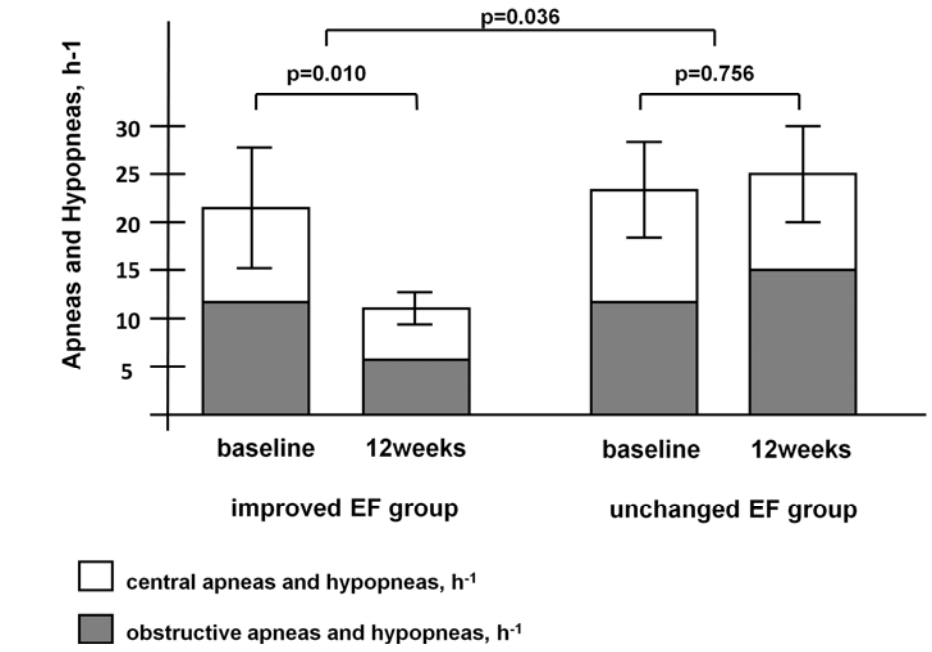

Figure 4. Change of $PaCO_2$ according to the change of cardiac function Abbreviations: improved EF group = improvement of left ventricular ejection fraction within 12 weeks after AMI by ≥5%; unchanged EF group = improvement of left ventricular ejection fraction within 12 weeks after AMI by <5%; $PaCO_2$ = arterialized capillary PCO_2

Figure 4

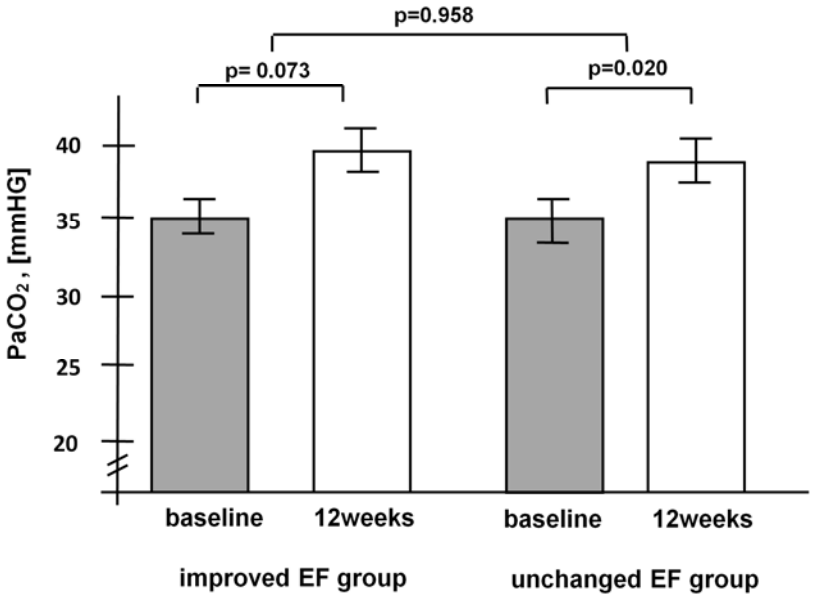
p=0.958
p= 0.073
p=0.020
40
35
30
25
20
PaCO2, [mmHG]
baseline
12weeks
baseline
12weeks
improved EF group
unchanged EF group

Table 1. Patient characteristics

	Improved EF	Unchanged EF	p-value
N	16	24	
age, [years]	55 ± 9	56 ± 11	0.755
Male gender, [%]	15 (94)	17 (71)	0.114
weight, [kg]	87 ± 11	84 ± 19	0.672
Body mass Index, [kg/m²]	28 ± 3	28 ± 4	0.506
Current smoking, [%]	8 (50)	15 (63)	0.936
Maximal Creatinine kinase, [U/l]	1820 ± 1471	1930 ± 1370	0.813
Troponin I, [ng/ml]	27 ± 81	36 ± 84	0.739
NT-pro BNP, [pg/ml]	1390 ± 1180	1693 ± 1720	0.546
Kreatinin, [mg/dl]	1 ± 0.4	1 ± 0.3	0.216
EF, [%]	43 ± 2	45 ± 2	0.421
Hypertension, [%]	9 (56)	13 (54)	0.897
Diabetes mellitus, [%]	4 (25)	3 (13)	0.308
Atrial fibrillation, [%]	1 (6)	0 (0)	0.215
AHI, [/h]	21 ± 14	22 ± 26	0.887
Obstructive AHI, [/h]	12 ± 10	10 ± 10	0.526

Abbreviations: AHI = apnea-hypopnea index; improved EF group = improvement of left ventricular ejection fraction within 12 weeks after AMI by ≥5%; unchanged EF group = improvement of left ventricular ejection fraction within 12 weeks after AMI by <5%; NT-pro BNP = n-terminal pro brain natriuretic peptide; EF = left ventricular ejection fraction

Table 2. Medication at baseline and follow up

	Improved EF	Unchanged EF	p-value
baseline			
ACE inhibitor/ AT1-antagonist, [%]	16 (100)	24 (100)	1.000
Beta-blocker [%]	16 (100)	23 (96)	0.408
Loop diuretics, [%]	2 (13)	5 (21)	0.497
Thiazide diuretics, [%]	3 (19)	4 (17)	0.865
12 weeks			
ACE inhibitor/ AT1-antagonist, [%]	14 (89)	22 (92)	0.455
Beta-blocker [%]	16 (100)	22 (92)	0.236
Loop diuretics, [%]	2 (13)	6 (26)	0.301
Thiazide diuretics, [%]	2 (13)	5 (22)	0.460

Table 3. Respiratory and sleep characteristics according to the change of cardiac function

	Improved EF			Unchanged EF			p-value
	Baseline	12 weeks	p-value	Baseline	12 weeks	p-value	
Respiratory characteristics							
AHI, [h^{-1}]	21±14	11±9	0.010	22±26	23±24	0.756	0.036
obstructive AHI, [h^{-1}]	12±10	6±4	0.008	10±10	14±19	0.166	0.009
central AHI, [h^{-1}]	10±12	6±6	0.342	12±23	6±10	0.287	0.906
$PaCO_2$, [mmHG]	35.2±4.2	37.6±3.6	0.073	35.2±2.2	37.6±3.4	0.002	0.958
SaO_2 mean, [%]	93.4±1.8	94.4±1.4	0.041	93.8±1.9	94.0±1.5	0.398	0.149
SaO_2 min, [%]	85.0 ±7.9	86.5±6.3	0.546	85.6±6.3	85.4±6.4	0.335	0.471
Sleep characteristics							
Sleep efficiency, [%]	76±1	74±1	0.544	70±1	70±1	0.135	0.150
N3, [%]	16±6	14±6	0.413	17±9	16±10	0.594	0.717
REM, [%]	17±6	15±7	0.394	16±8	14±7	0.097	0.757
ESS	8±5	7±3	0.886	7±4	6±3	0.617	0.821

Abbreviations: AHI = apnea-hypopnea index; $PaCO_2$ = awake arterialized capillary PCO_2; SaO_2 mean = mean oxygen saturation; SaO_2 min = minimal oxygen saturation; N3 = % of total sleep time spent in N3 sleep stage; REM = % of total sleep time spent in rapid eye movement sleep stage, ESS = Epworth Sleepiness Scale score