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Sleep apnea in patients with paroxysmal atrial fibrillation

Sleep apnea syndrome in patients with paroxysmal atrial fibrillation

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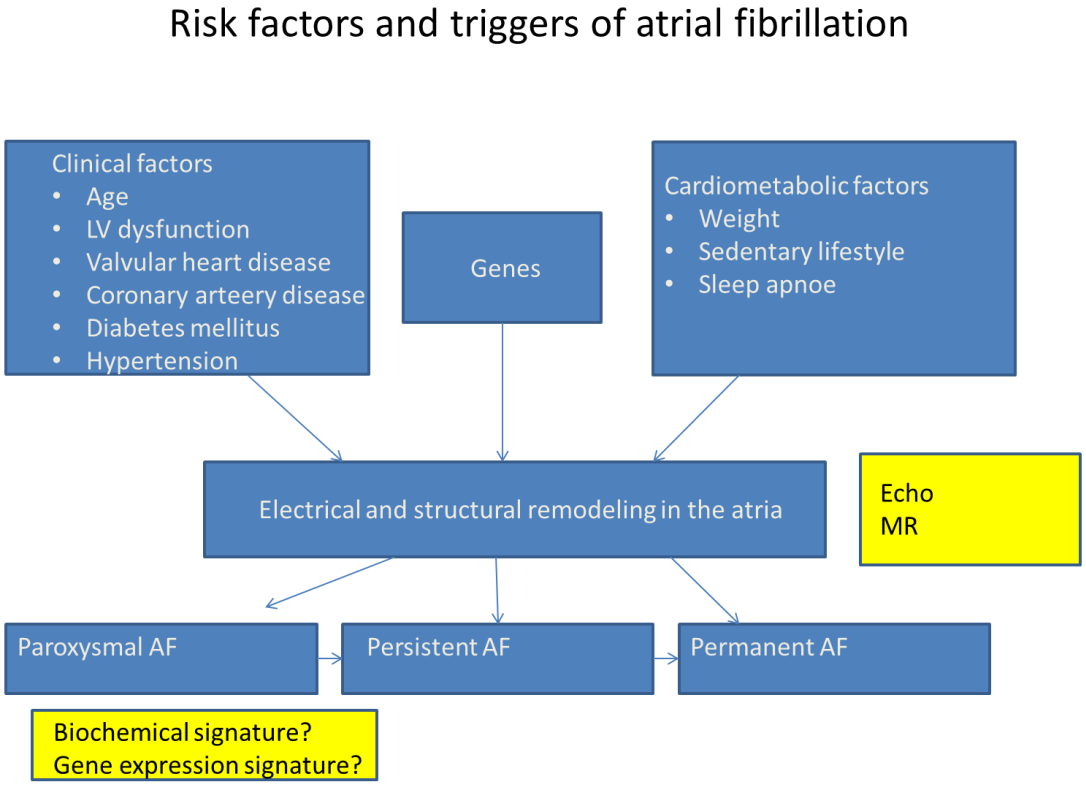
BACKGROUND

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disturbance in adults with a prevalence of around 2.5% among people above 40 years, rising to >10% in those greater than 80 years[1], with these values expected to rise significantly the coming decades. The occurrence of AF is associated with significantly increased mortality as well as morbidity of which cerebrovascular accidents is the most important. A substantial portion of AF is paroxysmal, and it is now established that the burden of AF is related to the risk of thromboembolic events[2], as well as symptom burden and quality of life. Despite AF being one the earliest recognized arrhythmias, treatment options remain limited. Several antiarrhythmic therapies are available, but many have limited efficacy and the potential for toxicity and adverse events are recognized. Recent year's catheter ablation of AF continues to gain acceptance with the main indication being the elimination of symptomatic AF when pharmacological agents are contraindicated or have failed. However the recurrence rate after ablation is high and a substantial portion is in the need of continuous pharmacological treatment as well as lifelong anticoagulation. The reason for the limited success of both pharmacological and ablation therapy is unclear, but may in large part be due to a limited insight into the pathophysiology of AF which is heterogeneous and complex. Well known associated factors leading to the development and progression of AF are age, left ventricular dysfunction, valvular heart disease, hypertension and diabetes mellitus. In addition recent data have suggested that several cardio metabolic factors such as sleep apnoe, obesity and sedentary life style are associated with adverse electrical and structural remodeling in AF (Figure). In support of this is randomized controlled trials demonstrating a benefit of weight reduction as well as exercise training[3].



Sleep apnea (SA) is a common chronic disorder both in the general population and among different patient groups, including cardiovascular (CV) disorders[4-6]. SA is usually divided into obstructive SA (OSA), central SA (CSA) and a combination. While OSA is caused by nocturnal upper airway collapse, CSA is a result of decreased ventilator drive mainly due to loss of fine tuning breathing control. SA is followed by a number of physiological and biochemical derangements where nocturnal oxygen desaturation and hyperapnia are central[7], followed by sympathetic activation[8,9], oxidative stress[10,11] and systemic inflammation[12-14] which have been shown to be the main intermediary mechanisms associated with the disorder.

The pathophysiological disturbances in SA contribute to electrical and myocardial remodeling which predisposes to different arrhythmias. There is now strong evidence for an association between AF and SA[15, 16,17], and different studies in AF patients have shown a prevalence of SA of 40-

75%[18]. Studies have also demonstrated that OSA diagnosis and severity are independently associated with incident AF[19] suggesting that treatment of OSA could reduce the clinical burden of AF. However, to what extent treatment of OSA will reduce the incidence of AF, or if it will improve the burden of arrhythmia among patients with AF is not established[20-22]. Thus, there is a need for comprehensive prospective randomized study to examine if the treatment of SA reduces the burden of AF.

The hypothesis for the present study is that treatment of SA reduces the burden of AF among patient with paroxysmal AF. To test the hypothesis we will perform a prospective randomized controlled study to examine the effect of SA treatment on the AF burden as assessed by an implanted monitor that continuously detect all episodes of arrhythmias.

HYPOTHESIS

The overall hypothesis of the present study is that there is a close correlation between AF with SA and that treatment of SA will reduce the overall burden of AF as well as reduce the amount of silent atrial fibrillation and recurrence of AF after pulmonary vein ablation.

AIMS

The overall aim of the study is to examine if treatment of SA reduces the burden of AF, but the design with continuous recording of the patient's rhythm with a Reveal allows more details examination of what triggers AF including sleep patterns. The specific aims are then:

Phase 1 (before ablation):

1. Examine if treatment of SA reduces AF burden in patients with paroxysmal atrial fibrillation

2. Examine if treatment of SA reduces AF burden in patients with paroxysmal atrial fibrillation as assessed by the Atrial Fibrillation Severity Scale (AFSS)

3. Examine if treatment of SA will improve quality of life (QoL) as assessed by SF-36

4. Examine if treatment of SA will improve sleep quality and obstructive sleep apnea symptoms as measured using the Epworth Sleepiness Scale (ESS) score, the Functional Outcomes of Sleep Questionnaire (FOSQ), the Berlin Questionnaire and the STOPBang Questionnaire.

5. Examine if sleep disordered breathing; i.e. OSA vs. CSA triggers onset of paroxysmal AF.

6. Examine if the AF alter gene expression, i.e. examine if the burden of AF is associated with a specific gene expression pattern as assessed by gene expression in leucocytes.

7. To examine if onset of paroxysmal AF is associated with specific activity patterns, as assessed by an activity registrator (Garmin Activity Watch or similar equipment)

8. To examine the relationship between structural remodeling in the heart (especially the atrium) using new echocardiographic modalities (strain, tissue doppler, 3D echo)

Phase 2 (after ablation):

9. Examine if treatment of SA will improve outcome after ablation with less episodes of silent AF as well as recurrence of AF

10. Examine if ablation in AF will improve sleep disordered breathing

11. Examine possible mechanism for treatment effect

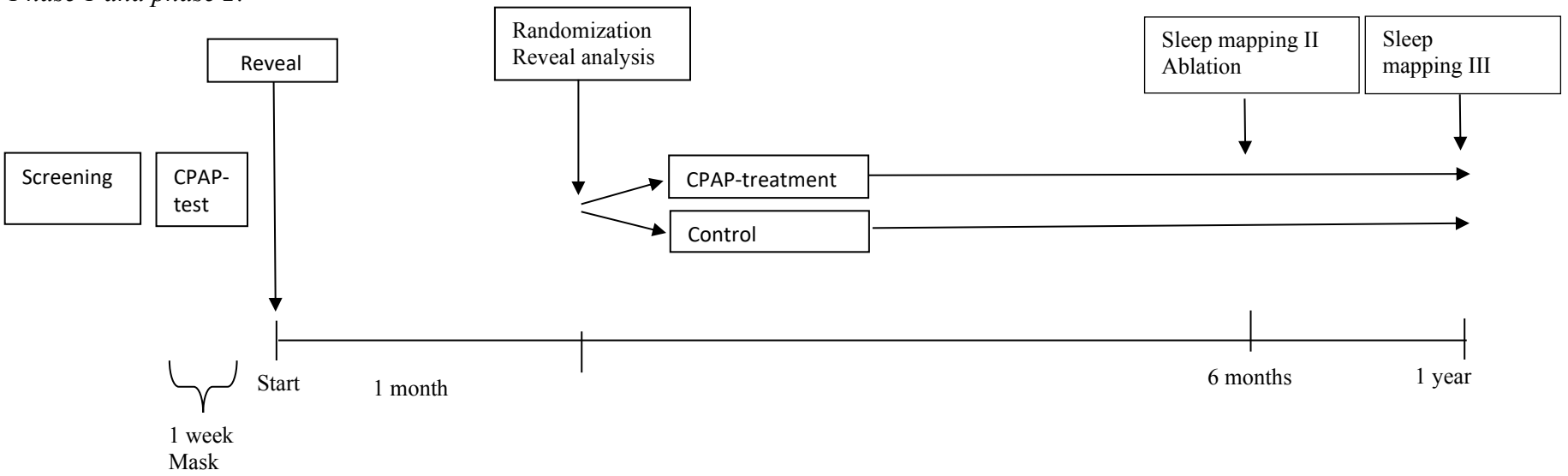
METHODS

4.1 Study design.

This is a prospective, open-label, randomized, parallel-group multicenter trial conducted at two centers, Oslo University hospital, Rikshospitalet and St.Olav. Patients with paroxysmal AF and concomitant SA will be studied. The effects of treating SA with a CPAP (Continuous positive airway pressure**)** or ASV (adaptive servo ventilation) compared with usual care on the burden of AF will be determined over a treatment period of 5 months.

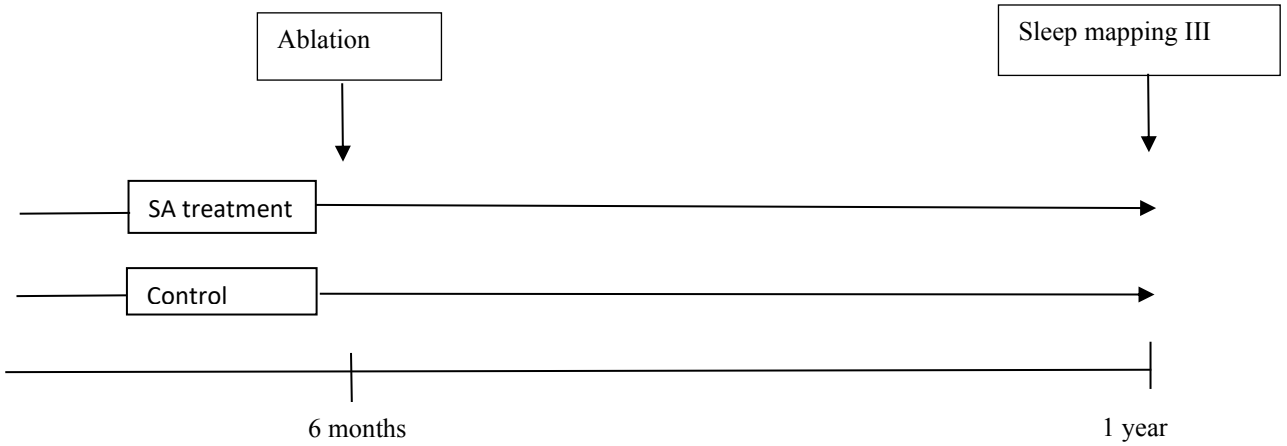
The study has the following steps: 1. All patients with paroxysmal AF will be screened for SA. 2. Those who have SA, defined as an AHI index ≥15 and who tolerate SA treatment, defined as using the mask > 4 hours a night during the tolerability test week, will have a Medtronic`s Reveal® Insertable Loop Recorder implanted. A subgroup of 10 patients with AHI<5 and 10 patients with AHI between 5 and 15 will also be included. 3. After 1 month of rhythm recording the patients will be randomized to SA-treatment or control. (CPAP or ASV depending on the average amount of CSA during the mask test week; i.e , cAI >10 will use ASV)

Phase 1 and phase 2:



Phase 2:

Phase 1 will be continued by a phase 2 study for patients scheduled for ablation. After 6 months all patients will have their scheduled treatment with catheter ablation and continue either their SA treatment or control for another 6 months. Reveal recordings will be analyzed every third month. The primary objective this phase is to examine if SA treatment reduces the recurrence rate after ablation.



4.2 Patients.

Patients with paroxysmal AF will be included.

Inclusion criteria:

- Age 18-75 years
- Male or female
- Patients with paroxysmal AF
- Moderate-to-severe SA defined as an AHI ≥15/h (OSA and/or CSA)
- Signed informed consent

Exclusion criteria :

- Unstable patient
- Patients with left ventricular ejection fraction (LV-EF) < 45%
- Unstable coronary artery disease or myocardial infarction within 3 months prior to the study
- ACB-operated within 6 months prior to study
- A myocardial infarction or PCI within 3 months prior to the study

- Patients with interstitial lung diseases, severe obstructive lung defects, and thoracic myopathies, patients with baseline SaO2 < 90 % and/or FEV1<50% pred
- Patients not beeing able to do CPAP-treatment/non-compliant patients.
- Patients with Transient Ischemic Attack (TIA) or stroke within three months prior to the study
- BMI > 40 kg/m2
- Drowsy drivers and/or sleepy patients with ESS (Epworth Sleepiness Score) >15
- Patients already using CPAP
- Patients with single chamber pacemaker
- Patients using amiodarone at inclusion

Sleep Mapping

All patients will undergo a sleep screening using a portable polygraph system at home. Nasal airflow, chest and abdominal effort, pulse oximetry and body position are recorded simultaneously. Automated analysis using standard software is used. In addition the analyses will be reviewed and corrected by an independent SDB specialist. Standard definitions will be used for the scoring of sleep disorders; hypopnea defined as a ≥ 30% reduction in airflow in combination with a drop in O2 saturation of ≥3%, apnea defined as a ≥ 90% reduction in airflow for ≥ 10 sec and classified as either obstructive (if accompanied by typical thoracic-abdominal breathing effort) or central (if there is no effort). The number of episodes of apnea-hypopnea per hour is referred to as apnea-hypopnea index (AHI). Patients with an index ≥15/h are included in the present study. Patients with two or more sleep mappings must have an average AHI ≥ 15/h to be included. During the sleep mapping oxygen saturation will be recorded.
All sleep recordings will be read in a core lab by persons unaware of treatment allocation.

Tolerability test: We know from previous trials that at least 20% of the population do not tolerate CPAP or ASV treatment for various reasons. In order to reduce the number of drop outs, a simple tolerability test will be performed prior to randomization. The patients will be asked to use an automatic CPAP machine every night for a week. The last night of tolerability test, oxygen saturation will be recorded as well. If mask treatment is tolerated they will be invited to participate. Compliance is defined as > 4 hours per night every night for 7 nights.

Reveal insertable cardiac monitor.
Recordings for occurrence of AF will be performed by an implantable cardiac monitor; Medtronic`s Reveal® Insertable Loop Recorder. The device is inserted subcutaneously, continuously records single-lead ECG and has an algorithm designed to detect AF by looking at the irregularity and incoherence of R-R intervals. A previous study has demonstrated the device ability to correctly identify AF in 96.1% of patients and to correctly exclude AF in 97.4% of patients[23]

4.3 Intervention
All participants will receive standardized education in habits that promote improved sleep quality and reduced cardiovascular risk including advice on diet and exercise

After baseline evaluation, a stratified permuted block design with stratification according to site will be used, and the patients randomized to one of two interventions: Active treatment for SA or just sleep education (controls).
Active treatment: Patients will be treated with automatic CPAP (Continuous positive airway pressure**)** (ResMed) which automatically adjusts pressure levels based on a patient`s breathing. The automatic CPAP is effective in treating obstructive sleep apnea by preventing the soft tissues of the upper airway from narrowing or collapsing. If the patients have central apneas in addition (average cAI >10 during mask test week) they will be treated with an ASV (adaptive servo-ventilation) (ResMed). The ASV device contains an algorithm which treats both obstructive and central sleep apnea. The patients will be followed by phone, rapid access to the clinic, and regular follow up (see flow chart). Patients with problems or non-compliant patients will be invited to the clinic for additional education and troubleshooting. Compliance is defined as > 4 hours per night.

Controls: No interventions besides education in healthy lifestyle and sleep education will be given

All patients will be followed closely by regular visits to the outpatient clinic or by phone. In addition they will be followed by telemonitoring to assess the patient’s treatment and compliance to the device.

Definition of outcome

Phase 1:

Primary outcome

- Reduction in total burden of AF (Reveal device date)

Secondary outcome after treatment of SA in AF study

- Reduction in recurrence rate of AF after ablation
- Reduction in AF symptom burden as assessed by Atrial Fibrillation Severity Scale (AFSS)
- Change in quality of life (QoL) as assessed by SF 36
- Change in sleep quality and symptoms of obstructive sleep apnea as measured using the Epworth Sleepiness Scale (ESS) score, the Functional Outcomes of Sleep Questionnaire (FOSQ) and the Berlin Questionnaire and Stop-Bang Questionnaire.
- Change in blood levels of catecholamine's, NT-proBNP, troponins and inflammatory and vasoactive substances
- Concordance in sleep date recorded from the PG and the Reveal device data

Echocardiography

Echocardiography will be used both for inclusion of patients (LV-EF>45%) and assessment of structural abnormalities of importance for AF will be given. In addition to standard recording, special emphasis on left atrium with strain and 3 D echocardiography will be performed

Atrial Fibrillation Severity Scale (AFSS).

AFSS is a validated scale that includes 3 domains of AF: frequency, duration and severity

Berlin Questionnaire

Symptoms of obstructive sleep apnea will be evaluated using the Berlin Questionnaire.

Stop-Bang Questionnaire

A questionnaire to screen patients for obstructive sleep apnea

Quality of life (QoL) and symptoms

QoL will be measured by the validated form of SF *36.*

Sleep Quality

The functional outcome of sleep treatment will be evaluated using the Epworth Sleepiness Scale (ESS) score and the Functional Outcomes of Sleep Questionnaire (FOSQ).

Activity recording

To get insight into factors triggering AF an Activity Watch will be used. It tracks the activity level by recording the patient's steps, logs the daily jog, and monitors the heart rate.

Biomarkers

Blood samples will be taken with the main purpose of answering the following questions:

1. Is there any evidence of abnormalities that trigger AF (for instance thyroid abnormalities, electrolyte abnormalities, renal insufficiency etc.)?
2. Are there any inflammatory variables associated with the burden of AF?
3. Is treatment of SA associated with changes of inflammatory variables?

Laboratory tests

- Regular screening: Hgb, white blood cells, platelets, CRP, creatinine, urea, uric acid, liver function, thyroid function, lipid status, glycemic control
- Additional analysis

- Inflammatory cytokines: e.g., TNF-α, sTNFR2, interleukin-6 (IL-6).
- Anti-inflammatory cytokines: e.g., IL-10
- Chemokine's: e.g., monocyte chemo attractant peptide-1 (MCP-1) and IL-8
- Regulators of matrix degradation: e.g., MMPs and their endogenous inhibitors TIMPs.
- Biochemical markers for endothelial function: Endothelin, von Willebrand factor
- Prothrombotic factors. Fibrinogen, plasminogen activator inhibitor-1
- NT-proBNP (Elecsys, Roche) is a sensitive marker of myocardial dilatation.

Gene expression analysis (optional)
Gene expression analysis of white blood cells will be done using real-time quantitative polymerase chain reaction (RT-PCR) and ribonuclease protection assay. The present study will investigate if:

1. Is paroxysmal AF associated with specific gene expression patterns?
2. Has SA treatment an impact on the pattern of gene expression and if this is related to reduction of atrial fibrillation burden.

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Statistics
Basic statistics: Both parametric and non-parametric statics will be used depending on distribution. Skewed variables will be analyzed by Kruskal Wallis, Friedmann, Mann-Whitney U or Wilcoxon Rank Sum and Spearman depending on design. Variables that are normally distributed will be analyzed by One-way and repeated measures ANOVA and paired and unpaired T-tests. Contingency statistics will be performed as appropriate.

Power calculation

AF study: The primary end point is a reduction of AF burden by 25 %. To what extent treatment of AF will improve SA is unclear, and there are few data on if treatment of SA improves the burden of arrhythmia among patients with AF. Among patient with paroxysmal AF, the total AF burden is highly variable. In the present study we have therefore not done a power analysis upfront, but will use a practical approach. Based upon a study at St Olav's Hospital (Jan Pål Loennechen, personal information) they have demonstrated an effect of exercise training compared with controls in a population of 50 patients with paroxysmal atrial fibrillation recorded with a Reveal Reorder. In order to increase the power of

secondary end points, we will include 100 patients. However, when approximately half of the population has been included, and more data of the burden of AF is available, we will conduct a formal power analysis, and from this estimate the final sample size.

ETHICS

Paroxysmal AF is associated with high morbidity of which stroke is the most feared complication. At present antiarrhythmic medication has limited efficacy and identification of alternative triggers and treatment warranted. The effect of SA on triggering AF has recently been recognized but the impact is unclear and if treatment helps is not precisely known. It is therefore important to increase the knowledge of these conditions and their underlying aggravating factors. All patients will be given informed consent.
The study will be applied to the Oslo University Hospital's ethic and data inspector (personvernombud). The study will be applied to the local ethics committee (Regional komité for medisinsk og helsefaglig forskningsetikk (REK) Sør-Øst) and Norwegian Social Science data services, and registered at ClinicalTrials.gov.

ORGANIZATION

The current project is based on a collaboration between Oslo University Hospital and St Olav Hospital, and within these institutions interdisciplinary collaboration which includes:

Department of Cardiology, Rikshospitalet. This department was rated "excellent" in 2003 and very good-excellent in the recent 2011 evaluation performed by the Norwegian Research Council.

- *Prof. Lars Gullestad* (Principal Investigator) has broad experience in cardiology and his group has an excellent track record in clinical research. His group currently consists of 3 postdoctoral fellows, 7 PhD students, 2 medical student researchers and a technical staff of 3.
- *Prof. Thor Edvardsen* is the head of the Department of Cardiology and head of the Center of Research-driven Innovation, and will contribute new analysis methods for the echocardiographic data.
- *Prof. Svend Aakhus* is an expert in clinical echocardiography, an important assessment technique in the proposed project. He will be responsible for the core echocardiography laboratory
- *Ole-Gunnar Anfinsen* is an electrophysiologist and will together with EL be responsible for Reveal implantation and follow-up
- *Erik Lyseggen* is an electrophysiologist and will together with EK be responsible for Reveal implantation and follow-up

Department of Cardiology, St.Olavs Hospital.

- *Jan Pål Loennechen* (will be the responsible person at this institutions) has broad experience in cardiology and works as an electrophysiologist. He is leading a research group and has recently conducted a study looking at the effect of exercise training in patients with paroxysmal atrial fibrillation.
- Sigurd Loe Stenshamn has broad experience in pulmonary-and sleep medicine.
- Lars Aakerøy is engaged as a PhD student

Other central collaborators in the current project will be:

- *Hassan Z. Khiabani, Clinical Trial Unit,* and Department of Pharmacology will take active part in the study and examination of sleep patterns will be performed in his department.
- *Prof. Harriet Akre*, Department of Otorhinolaryngology, Head &Neck Surgery has broad experience in sleep medicine.
- *Prof. Pål Aukrust Section of Clinical Immunology and Infectious Disease* (, MD, PhD) is together with Thor Ueland responsible for gene expression patterns and inflammatory variables
- *Professor Thor Ueland, Research Institute for Internal Medicine:* will be responsible for measurement of inflammatory cytokine and vasoactive peptide levels, and gene expression studies.
- *Unit of Biostatistics and Epidemiology*, Ragnhild S. Falk, MSc PhD.

Role of the PhD student at Rikshospitalet. Gunn Marit Traaen, MD, is engaged as a PhD student. She will recruit patients and take part in SA recordings, patient follow-up, data gathering, and writing of papers. It is anticipated that the following papers will be included in the thesis:

1. The prevalence of SA in patients with paroxysmal AF
2. The effect of SA treatment on the AF burden
3. The impact of normalized rhythm on sleep disordered breathing

SCIENTIFIC IMPORTANCE

The aim of the present project is to substantially advance our understanding of the interaction between SA and AF that will aid in the decision making process how to treat these patients with the aim of better outcome of the patients. In addition, given the advantage of continuous recording of the patient's heart rhythm, the present study will examine possible triggers of AF such as activity level and inflammatory substances, and examine the role of structural abnormalities in the heart as assessed by echocardiography and MRI for the triggering of AF episodes. An overall aim is therefore a better phenotyping of the patient which could aid in a more person-specific treatment approach. The primary recipient of the insights obtained is the scientific community, and peer-reviewed scientific journals of high quality will be the primary channel for communicating the results. In particular, we will give high priority to publish in high impact journals (i.e., 2A journals), rather than the number of published papers. In addition, the results will be presented at scientific meetings.

PLAN FOR PROGRESS

	2015	2016	2017
Inclusion	X	X	
Data analyses		X	X
Publication		X	X

APPENDIX
Flow chart in AF studies (phase 1 and phase 2)

	Screening	Tolerability test CPAP 1 week	Reveal Implantation Time=0	Randomi-zation 1 month	Phone Calls*	3 months/ 2 months after random.	6 months preablation	9 months/ 3 months post ablation	12 months/ 6 months post ablation
Informed consent	X								
Physical examination			X				X		X
Tolerability/AE/SAE		X			X	X	X	X	X
ECG, BP, HR			X				X		X
Alcohol questionnaire	X		X	X		X	X	X	X
Questionnaires	X						X		X
Sleep scoring/polygraph data	X						X		X
Echocardiography TT			X				X		X
TEE							X		
Routine Lab		X					X		X
Cytokines and vasoactive peptides		X					X		X
Gene expression		X					X		X
Reveal device data				X		X	X	X	X

References

1. Lloyd Jones Circulation 121:948

2. Glotzer Circ Arrhythmia Electrophysiol 2009;2:474

3. Jan Pål Loennechen; abstract 2015

4. Duran J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. Am J Respir Crit Care Med 2001; 163(3 Pt 1):685-689.

5. Naughton MT. Sleep disorders in patients with congestive heart failure. Curr Opin Pulm Med 2003; 9(6):453-458.

6. Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Topfer V. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. Eur J Heart Fail 2007; 9(3):251-257.

7. Zamarron C, Valdes CL, varez-Sala R. Pathophysiologic mechanisms of cardiovascular disease in obstructive sleep apnea syndrome. Pulm Med 2013; 2013:521087.

8. Imadojemu VA, Mawji Z, Kunselman A, Gray KS, Hogeman CS, Leuenberger UA. Sympathetic chemoreflex responses in obstructive sleep apnea and effects of continuous positive airway pressure therapy. Chest 2007; 131(5):1406-1413.

9. Somers VK, Mark AL, Abboud FM. Sympathetic activation by hypoxia and hypercapnia--implications for sleep apnea. Clin Exp Hypertens A 1988; 10 Suppl 1:413-422.

10. Carpagnano GE, Kharitonov SA, Resta O, Foschino-Barbaro MP, Gramiccioni E, Barnes PJ. 8-Isoprostane, a marker of oxidative stress, is increased in exhaled breath condensate of patients with obstructive sleep apnea after night and is reduced by continuous positive airway pressure therapy. Chest 2003; 124(4):1386-1392.

11. Lavie L. Obstructive sleep apnoea syndrome--an oxidative stress disorder. Sleep Med Rev 2003; 7(1):35-51.

12. Arias MA, Garcia-Rio F, onso-Fernandez A et al. CPAP decreases plasma levels of soluble tumour necrosis factor-alpha receptor 1 in obstructive sleep apnoea. Eur Respir J 2008; 32(4):1009-1015.

13. Carpagnano GE, Spanevello A, Sabato R et al. Systemic and airway inflammation in sleep apnea and obesity: the role of ICAM-1 and IL-8. Transl Res 2010; 155(1):35-43.

14. Steiropoulos P, Kotsianidis I, Nena E et al. Long-term effect of continuous positive airway pressure therapy on inflammation markers of patients with obstructive sleep apnea syndrome. Sleep 2009; 32(4):537-543.

15. Gami AS, Hodge DO, Herges RM et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. J Am Coll Cardiol 2007; 49(5):565-571.

16. Patel D, Mohanty P, Di BL et al. Safety and efficacy of pulmonary vein antral isolation in patients with obstructive sleep apnea: the impact of continuous positive airway pressure. Circ Arrhythm Electrophysiol 2010; 3(5):445-451.

17. Gami AS, Pressman G, Caples SM et al. Association of atrial fibrillation and obstructive sleep apnea. Circulation 2004; 110(4):364-367.

18. Somers VK, White DP, Amin R et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. J Am Coll Cardiol 2008; 52(8):686-717.

19. G Cadby et al

20. Fein AS, Shvilkin A, Shah D et al. Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence after catheter ablation. J Am Coll Cardiol 2013; 62(4):300-305.

21. Naruse Y, Tada H, Satoh M et al. Radiofrequency catheter ablation of persistent atrial fibrillation decreases a sleep-disordered breathing parameter during a short follow-up period. Circ J 2012; 76(9):2096-2103.

22. Naruse Y, Tada H, Satoh M et al. Concomitant obstructive sleep apnea increases the recurrence of atrial fibrillation following radiofrequency catheter ablation of atrial fibrillation: clinical impact of continuous positive airway pressure therapy. Heart Rhythm 2013; 10(3):331-337.

23. Hindrics G Circ Arrhythm Electrophysiol 2010;3:141