UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 05/11/2011

1. PROJECT TITLE

Right Ventricular Hemodynamics using Cardiac MRI in COPD Patients with OSA

2. PRINCIPAL INVESTIGATOR

Atul Malhotra, MD

3. FACILITIES

UCSD, Clinical Teaching Facility – Sleep Laboratory

4. ESTIMATED DURATION OF THE STUDY

July 2014 through June 2016

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

The coexistence of chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) in the same patient has been termed overlap syndrome, affecting 1% of the U.S. population. Despite the high prevalence of overlap syndrome, few data are available on its pathophysiological and clinical consequences. Overlap syndrome has recently been reported to have excess mortality compared with COPD alone. Thus study of overlap syndrome patients may be useful toward understanding the underlying pathways. No study has evaluated the mechanisms of excess cardiovascular mortality in untreated overlap syndrome. Also, no prospective, randomized, controlled data are available on treatment of overlap syndrome. Thus, we propose to conduct this prospective, randomized, controlled pilot study that aims: (1) to compare right and left ventricular hemodynamic parameters using cardiac MRI in overlap syndrome vs. COPD only and OSA only; (2) to compare the effects of bi-level positive airway pressure (BiLevelPAP) vs. nocturnal oxygen therapy (NOT) on right ventricular (RV) hemodynamics in overlap syndrome. This will allow us to test the hypothesis that treatment of both hypoxemia and hypercapnia during sleep will improve RV hemodynamics compared with treatment of hypoxemia alone in patients with overlap syndrome. Potential benefits to patients and society will include better understanding of the mechanisms of cardiovascular mortality in overlap syndrome. We believe that these data will encourage use of PAP therapy in COPD patients with overlap syndrome if we observe significant improvement. We also plan a larger multi-center trial if this study provides encouraging preliminary data.

6. SPECIFIC AIMS

Study Aims:

a) To compare right and left ventricular (LV) hemodynamic parameters using cardiac MRI in overlap syndrome vs. COPD only and OSA only in a cross-sectional study;
b) To explore mechanisms of cardiovascular dysfunction in overlap syndrome;
c) To conduct a pilot clinical trial to compare the effects of BPAP vs. nocturnal oxygen therapy (NOT) on RV hemodynamic parameters in overlap syndrome (20 subjects in each arm) to establish feasibility.

We hypothesize that:

a) Patients with overlap syndrome have more RV dysfunction than those with COPD only or OSA only;
b) Treatment of both hypoxemia and hypercapnia plus catecholamine surges will improve RV hemodynamic parameters compared with treatment of hypoxemia alone in patients with overlap syndrome.

7. BACKGROUND AND SIGNIFICANCE

Prevalence and clinical significance of overlap syndrome

COPD and OSA are both common diseases affecting 10-20% and 5% respectively of the adult population over 40 years of age2. Both disorders carry considerable morbidity and mortality. Their coexistence in the same patient, termed overlap syndrome, is a common occurrence and may affect 1% of the U.S. population. A prospective, observational study found that all-cause mortality was 42.2% in the untreated (no CPAP) overlap syndrome group, significantly higher than in the COPD-only group (24.2%) after a median follow-up of over 9 years. Overlap syndrome is also associated with higher a risk of hospitalization for COPD exacerbation (relative risk 1.70) compared with COPD-only patients. Thus, it is important to know the mechanisms of mortality and the optimal treatment modality in this common disease.

Pulmonary hypertension (PH) and RV dysfunction in overlap syndrome

The high mortality in untreated overlap syndrome patients is due to cardiovascular mortality, but the exact mechanisms are not yet known. However, some evidence suggests that pulmonary vasoconstriction and RV dysfunction may be an underlying mechanism. The prevalence of PH in overlap syndrome is much higher than in OSA alone. PH and RV dysfunction are associated with poor prognosis in COPD. The 5-year survival rate is only 36% in those whose initial mean pulmonary artery pressure (mPAP) is >25 mm Hg compared with 66% in those whose initial mPAP is <25 mm Hg. Moreover, severity of PH correlates negatively with survival (5-year survival ~15% with mPAP > 40 mm Hg vs ~55% with mPAP 20–40 mmHg). On the other hand, RV dysfunction and hypertrophy have also been described in otherwise uncomplicated OSA (figure 2). Although RV function can be abnormal in either disease, it may be worse in overlap syndrome due to the increased burden of hypoxemia and hypercapnia. However, the changes in RV function have not been well studied in patients with overlap syndrome. In addition, endothelial dysfunction of pulmonary vasculature plays an integral role in the pathogenesis of pulmonary hypertension (PH). The gold standard for early detection of endothelial dysfunction requires intracoronary or intra-brachial infusions of vasoactive agents. However, it is invasive with potential side effects of vascular or nerve injuries. Recently, several non-invasive techniques have been developed to assess endothelial function and one of them is peripheral arterial tonometry (PAT) in response to reactive hyperaemia. This technique evaluates the percentage change of flow from baseline to the maximum flow during reactive hyperaemia following a five minute ischemia of the distal forearm (achieved by blowing up a blood pressure cuff around the arm). The advantage of this technique is non-invasive, simple, and reproducible with less observer dependence comparing to ultrasound based technique. Therefore, we choose to use this technique to evaluate the endothelial function in this study. Furthermore, recognizing that COPD and OSA are both important contributors to secondary PH, clinicians would likely treat both underlying diseases. With COPD, long-term oxygen therapy can improve COPD mortality. In OSA, continuous PAP (CPAP) therapy can improve PH. However, there is no rigorous research on how patients with overlap syndrome should be treated.

Rationale for using cardiac MRI to measure cardiac hemodynamic parameters

One way to measure the short term impact of any therapy on the cardiovascular system is with cardiac magnetic resonance imaging (MRI), which has been shown to be sensitive in measuring RV hemodynamic parameters. Furthermore, cardiac MRI findings correlate with clinical changes and can have prognostic value in PH. Compared to standard, 2–dimensional echocardiography, cardiac MRI has been shown to be superior in detecting regional wall motion abnormalities, RV function, size and muscle mass. Cardiac MRI also offers advantages over echocardiography since obesity or emphysema do not interfere with the MRI image quality and thus interpretation. A recent pilot study using cardiac MRI demonstrated RV remodeling in overlap syndrome patients compared with COPD patients, further confirming the utility of this modality. Another pilot study detects early fibrosis changes of extracellular volume (ECV) mapping techniques in COPD patients. Thus, we believe that cardiac MRI may be the preferred technique to assess pulmonary hemodynamics and RV function in patients with COPD and OSA overlap syndrome.

Overlap Syndrome and Upper Airway Inflammation

Obstructive sleep apnea is characterized by a recurrent collapse of the upper airway which has been shown to be associated with an increase inflammatory cells in surgical samples from the uvula, pharyngeal and nasal mucosa, and upper airway muscle. COPD is also characterized chronic inflammation of upper and lower airways, which was initially triggered by smoking. Since recent evidence demonstrated that exacerbation of COPD is associated with increased inflammation of both upper and lower airways, upper airway inflammation from OSA in patients with overlap syndrome (coexistence of OSA and COPD) may contribute to worse COPD prognosis comparing to patients with COPD alone. However, there is limited research in upper airway inflammation of patients with overlap syndrome at present time and more research is warranted. A minimally invasive technique, pharyngeal lavage, has been recently developed to assess mucosal inflammation of the upper airways in normal, OSA, and heavy snoring patients. With this new technique, we believe that we could further characterize the upper airway inflammation and potential pathophysiology in patients with overlap syndrome.

Positive airway pressure therapy in COPD

Treatment of hypoxemia in COPD alone has been shown to improve mortality. However, treatment of hypercapnia in COPD with nocturnal Bilevel has shown contradictory results. Of note, known OSA was excluded from the bulk of these above cited COPD studies. We postulate that COPD patients with concomitant OSA may be ideal candidates for positive pressure ventilation, since this intervention could treat both hypoxemia and hypercapnia.

Positive airway pressure therapy in overlap syndrome

Overlap syndrome patients are typically hypercapnic at more preserved levels of lung function than those with COPD alone (average forced expiratory volume in one second, FEV1 1.8 vs. 1.0 L). Therefore, overlap syndrome patients are likely to be particularly susceptible to pulmonary artery vasoconstriction due to intermittent hypoxemia and hypercapnia. OSA causes pharyngeal obstruction resulting in intermittent hypercapnia and hypoxemia. Accessory respiratory muscle atonia during REM sleep in patients with underlying COPD commonly leads to hypercapnia. By decreasing hypoxemia and hypercapnia, with resultant reduction of pulmonary artery vasoconstriction, treatment of overlap syndrome at night may well improve RV

(and LV) performance during the daytime. One uncontrolled study showed an improvement in gas exchange and FEV1 with CPAP therapy in overlap syndrome. Another prospective study showed a reduction in mortality and hospitalizations due to COPD exacerbations after CPAP therapy in overlap syndrome. Furthermore, we recently observed in 11,000 patients improved mortality in a dose response relationship with CPAP use in patients with overlap syndrome, although again lack of randomization limits definitive conclusions. To date, no prospective, randomized, controlled study has yet evaluated the effect of BiLevel therapy on clinical outcomes in overlap syndrome.

Rationale for using BiLevel vs. NOT

BiLevel can treat both hypoxemia and hypercapnia. We will use BiLevel to treat OSA in COPD patients rather than conventional CPAP therapy because COPD patients are prone to hypoventilation during sleep (especially REM sleep) due to atonic accessory respiratory muscles. Nocturnal oxygen therapy (NOT) corrects nocturnal hypoxemia. NOT will be used in the control group because recurrent transient hypoxemia during sleep is frequent in patients with COPD, and nocturnal desaturation during sleep is an independent risk factor for increased cardiovascular complications. Previous studies of oxygen therapy in COPD have shown that NOT is safe, even in hypercapnic COPD patients. CPAP, however, has less predictable effects on hypoxemia or hypercapnia in overlap syndrome patients. Thus, by comparing BiLevel vs. NOT, we can independently assess the effect of sleep-related hypercapnia on RV hemodynamics. Also, it will allow us to test the hypothesis that treatment of both hypoxemia and hypercapnia will improve RV hemodynamic parameters compared with treatment of hypoxemia alone in patients with overlap syndrome.

Limitations of prior literature

Though it is known that untreated overlap syndrome has increased cardiovascular mortality compared to COPD, the mechanisms of cardiovascular dysfunction in overlap syndrome have not been studied. Moreover, prospective, randomized, controlled trials of BPAP therapy in overlap syndrome are lacking. Our study will provide insight into mechanisms of excess cardiovascular mortality in overlap syndrome. The interventional part of our study is a pilot study to help determine optimal treatment of overlap syndrome patients. The preliminary data, if encouraging, will be used to plan a larger multi-center clinical trial with longer duration of BiLevel therapy (with mortality, hospitalizations and COPD exacerbations as outcomes).

8. PROGRESS REPORT

N/A

9. RESEARCH DESIGN AND METHODS

Part One Study Objective: The first part is a cross-sectional cohort study comparing subjects with overlap syndrome to those with COPD alone and those with OSA alone.

Subjects: Our target sample will be 150 subjects in the overlap syndrome group. This group will include subjects with age > 18 years with known or suspected diagnosis of overlap syndrome, which we will define as COPD: Global Obstructive Lung Disease (GOLD) stage 2 disease or higher and OSA: apnea-hypopnea index (AHI) >15/hour. We will exclude patients already using oxygen or BiLevel/CPAP, patients with known or suspected renal failure (creatinine >1.5 mg/dl), pregnant women (due to possible risk to the fetus due to cardiac MRI and gadolinium contrast), patients with atrial fibrillation or frequent (>10/h) premature ventricular contractions (since these may complicate cardiac MRI sequences) and patients with known contraindications to

MRI: metallic (ferromagnetic) implants, cardiac pacemakers, past history of claustrophobia.
The control subjects will be divided into two groups, one with COPD only (50 subjects) and the other with OSA only (50 subjects). The COPD control group will include subjects with known COPD diagnosed by a pulmonologist (GOLD stage 2 or higher). The OSA control group will include subjects with a known diagnosis of OSA diagnosed by a sleep specialist (apnea-hypopnea index, AHI >15/hour). The exclusion criteria for the control subjects will be the same as the overlap syndrome subjects.

Study enrollment: All patients will be recruited through the outpatient pulmonary and sleep medicine clinics at the UCSD hospitals. Poster advertisements will be placed in the outpatient clinics to encourage subject recruitment through physician referral. COPD patients in outpatient pulmonology clinics who express interest in enrolling in the study will be approached by one of the study investigators to obtain informed consent. COPD patients meeting eligibility criteria will be screened for OSA risk and scheduled for overnight polysomnography (PSG) as part of baseline visit. COPD patients with coexisting OSA will be enrolled in the overlap syndrome group. COPD patients without coexisting OSA will be enrolled in the COPD only control group. If COPD patients are referred for clinically indicated sleep studies, these patients will also be eligible for participation (as either COPD only or overlap syndrome patients), depending on the results of the sleep study.

Baseline visit: At the baseline visit, all 3 groups (overlap syndrome, COPD only and OSA only) will undergo a baseline PSG and measurement of body weight and height to calculate body mass index (BMI). Cardiac MRI will be done to measure RV and LV hemodynamics. Data regarding RV function with RVEDV (primary end-point), RVESV, RVEF, RV mass index, right atrial pressure, PA pressure and blood flow, indices of RV geometry, thickness and interdependence, as well as LV function including LVEDV, LVESV, LVEF, LV mass index, LV wall motion, extracellular volume (ECV) and coronary blood flow will be collected. Phlebotomy will be done to take blood samples for complete blood cell counts (with differentials), renal profiles, venous gas analysis, and exploratory analyses of inflammatory biomarkers and cytokines (CRP, TNF-alpha, IL-6, P-selectin, ICAM-1). Overnight urine samples will be collected to measure catecholamine excretion levels (epinephrine, norepinephrine, metanephrine, normetanephrine). Endothelium function will be evaluated through the non-invasive finger probes of the EndoPAT 2000 device (Itamar Medical, Caesarea, Israel). EndoPAT device measures digital pulse amplitude with the probes placed on the tips of both index fingers in reaction to temporary occlusion of arterial blood flow (achieved by blowing up a blood pressure cuff around the arm) for 5 minutes. Assessment of exercise capacity will be done using six-minute-walk-distance (6MWD) test. Saint George Respiratory Questionnaire (SGRQ) score and SF-36 Questionnaire will be used to assess health-related quality of life (HRQOL). The modified Medical Research Council (MMRC) score will be used to assess severity of dyspnea. The Epworth Sleepiness Scale (ESS) and Pittsburg Sleep Quality Index (PSQI) will be used to assess sleep quality and relevant symptoms. Assessment of upper airway inflammation will be done with a minimally invasive technique, pharyngeal lavage, immediately before and after the sleep study. To collect pharyngeal lavage samples, subjects simply gurgle 45 ml of sterile saline in 15 ml increments for 10 seconds, then spit the saline for collection and analysis. The pharyngeal lavage fluid will be used to analyze cell counts with differential and the remaining will be frozen for later analysis of inflammatory biomarkers. Assessment of cognitive function will be done using psychomotor vigilance task (PVT) and motor sequence task (MVT) by a computer program. Pulmonary function tests (PFTs) will be performed using the American Thoracic Society (ATS) criteria. BODE index (COPD mortality risk index predictor) will be calculated from these parameters listed above. The MRI will be scheduled as soon as available after the overnight sleep study. The time commitment for the sleep study will be 10 hours. The time commitment for the pulmonary function test will be 1 hour. The time commitment for the MRI is typically 30-40 minutes. In total, the time commitment to complete all of the required procedures of the Baseline Visit is approximately 12 hours.

Part Two Study Objective: The second part of the study is a prospective, parallel-group, randomized, controlled pilot study examining the effect of BiLevel therapy (and NOT if needed) vs. NOT alone in patients with overlap syndrome (20 subjects in each treatment arm).

Study Intervention: This will be done in 40 subjects in overlap syndrome group only who provide informed consent (20 subjects in each treatment arm). Randomization of overlap syndrome subjects to nocturnal BiLevel therapy (plus oxygen if needed based on saturations <88% while on stable bi-level settings), and NOT only will be done using sequentially-numbered, opaque, sealed envelopes using 1:1 allocation ratio. Regular therapy with COPD medications including long-acting anticholinergic medications and inhaled corticosteroids will be continued as advised by the treating pulmonologist. Only COPD subjects with stable clinical course during the duration of study intervention will be called for follow-up visits as any COPD exacerbations during the course of study intervention may potentially confound the follow-up study results. The time commitment for this initial visit will require up to 2-3 hours of the subjects time.

Follow-up visits: The first follow-up visit will be done 2 weeks after starting treatment to ensure compliance and determine any discomforts due to treatment. At this visit phlebotomy will be done to take blood samples for venous gas analysis. Subjects will be asked to complete all questionnaires as outlined in the baseline visit. Second follow-up visit will be done 3 months after starting treatment to ensure compliance with treatment and determine any study related discomforts. Subjects will be asked to complete all questionnaires and cognitive function testing as outlined in the baseline visit. The final follow-up visit will be done 6 months after starting study treatment. Throughout the course of the study, regular telephone contact will be maintained by the study stuff to ensure adherence to therapy and to address issues as they arise. At this final follow-up visit, all the tests done at baseline visit (except PSG) will be repeated as well as all afore mentioned questionnaires and cognitive function testing. This pilot study will generate preliminary data for a multi-center clinical trial with longer duration of PAP therapy and mortality, hospitalizations or COPD exacerbations as outcomes, if we find encouraging results. If the subject is called for follow-up visits, first follow up visit will require a time commitment of 15-20 minutes (2 week mark of starting treatment) for and the other two follow up visit will require a time commitment of 25-30 minutes (one at the 3-month mark of starting treatment and one final follow up visit). During the course of the 2 week, 3 month and 6 month periods between follow up visits, study staff may contact the patient to ensure adherence to therapy and address issues as they arise. While these phone call encounters may vary in time based on the subject's needs, typically they should require no more than 5-10 minutes of the subject's time.

Study endpoints: Primary endpoint: RVEDV (estimated by cardiac MRI) across the three study groups, and following intervention in the overlap syndrome patients in the randomized trial. Secondary endpoints: RVESV, RVEF, RV mass index, right atrial pressure, PA pressure and blood flow, indices of RV geometry, thickness and interdependence, LVEDV, LVESV, LVEF, LV wall motion, , extracellular volume, coronary blood flow, endothelial function (EndoPAT), serum complete blood cell counts (with differentials), serum renal profiles, pharyngeal lavage cell counts and differentials, serum and pharyngeal lavage inflammatory biomarkers (CRP, TNF-alpha, IL-6, P-selectin, ICAM-1), sympathetic activity (measured by urinary catecholamine excretion), HRQOL score and BODE index.

To offset transportation costs, parking costs and use of the volunteer's time, subjects will receive $150.00 for the overnight sleep study and an additional $100.00 for the MRI for a total of $250.00 upon completion of all tests in Part I. Study staff might ask the subject to return for a second overnight sleep study visit in the event the

data is of poor signal quality or we were unable to obtain sufficient data to complete analysis. If the subject agrees to return for a repeat study, he/she will be compensated $150.00 for their time and transportation.

10. HUMAN SUBJECTS

We anticipate recruiting a total of 150 patients for phase one study: 50 patients with overlap syndrome, 50 patients with COPD, and 50 patients with OSA, age and gender matched to the overlap syndrome patients. For the phase two study, we aim to recruit 40 patients among the overlap syndrome patients who participated in phase one.

Phase One Study:

This group will include subjects with age > 18 years with known or suspected diagnosis of overlap syndrome, which we will define as COPD: Global Obstructive Lung Disease (GOLD) stage 2 disease or higher and OSA: apnea-hypopnea index (AHI) >15/hour. We will exclude patients already using oxygen or BiLevel/CPAP, patients with known or suspected renal failure (creatinine >1.5 mg/dl), pregnant women (due to possible risk to the fetus due to cardiac MRI and gadolinium contrast), patients with atrial fibrillation or frequent (>10/h) premature ventricular contractions (since these may complicate cardiac MRI sequences) and patients with known contraindications to MRI: metallic (ferromagnetic) implants, cardiac pacemakers, past history of claustrophobia. The control subjects will be divided into two groups, one with COPD only (50 subjects) and the other with OSA only (50 subjects). The COPD control group will include subjects with known COPD diagnosed by a pulmonologist (GOLD stage 2 or higher). The OSA control group will include subjects with a known diagnosis of OSA diagnosed by a sleep specialist (apnea-hypopnea index, AHI >15/hour). The exclusion criteria for the control subjects will be the same as the overlap syndrome subjects.

Phase Two Study:

40 patients in overlap syndrome group recruited during phase one study will be invited to participate in phase two study. The overlap syndrome patients who provide informed consent will be randomized into the two treatment arms (20 subjects in each treatment arm).

11. RECRUITMENT

The studies will be conducted during wakefulness and sleep in normal subjects, those with COPD and OSA. Males and females (18-79 years) will be studied. Equal numbers of men and women with OSA and controls will be recruited by research staff from the CTF Sleep Laboratory. Subjects will be recruited after they initiate contact in response to IRB approved standard posters, newspaper advertisements, and/or flyers. Subjects who initiate first contact will be followed up with a telephone screening to ensure they qualify for participation in the study. Patients who have indicated they would like to be involved in research to their primary care physician and verbally consented to being contacted for this purpose will be approached directly by a research coordinator. All participants will have an “opt-out” provision to avoid any possibility of coercion. Advertisement for this study will also be placed in appropriate locations in English and Spanish. Finally, if we sometimes have difficulty recruiting people of Hispanic ethnicity, advertisements will also be placed in regions of the community with a high Hispanic population. Recruitment advertisement text previously provided will be utilized for all modes of recruitment mentioned previously. If the provided text is to be changed, each recruitment item will be submitted to IRB for review and reapproval.

A flyer describing the study will also be placed in the waiting room of the UCSD Sleep and Pulmonary Clinic. Subjects will be screened for snoring (historically), body mass index (BMI), and history of COPD.

ResearchMatch will be used to contact prospective participants with IRB approved recruitment message, which is on a separate page labeled "ResearchMatch Message to Potential Participants."

Spanish translated flyers and advertisements will be submitted after approval of the English documents.

12. INFORMED CONSENT

A waiver of documented consent will be requested and once oral consent by the subject is obtained this consent will be used for the sole purpose of discussing the study with the subjects over the phone and performing the screening process as needed. The reason for this is because the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. In an effort to further protect the subject and their right to privacy, subjects will be screened for qualification prior to being asked to sign a written consent form to participate in the research project. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. Additionally, the screening process presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required.

Once oral consent has been obtained, a research coordinator will screen the subjects over the telephone. Individuals interested in participating in this study will be given detailed explanation of the procedures, potential benefits, risks and discomforts of the study by the study researchers. A copy of the consent form will be mailed a minimum of 48 hours in advance to the individuals interested in participating in the study. The PI will obtain informed, written consent on the day of the study after ensuring the patients fully understand the procedures and risks/benefits. Subjects unable to give their own consent will not be included in the study. Subjects who have given a written consent will be given a copy of the signed consent form. The original consent will be kept in the subjects research file in a locked cabinet.

They will also be informed that participation in the registry is completely voluntary and will not directly impact the care that they receive at UCSD. Informed consent will be obtained in English for all English speakers. For patients who are not English speakers, consent will only be obtained in Spanish by a Spanish speaking provider or certified interpreter (in person or over the telephone). Documents will be used that are in the subject's primary language. Patients will be told that continued, qualified interpretative services to the participant will be provided.

Original consent forms will be kept on file by the study coordinator in the master research file. A copy of each will also be scanned into the patient's electronic medical record in the "media" tab where other consent forms can be found.

Spanish translated documents will be submitted to the IRB after approval of the English documents.

13. ALTERNATIVES TO STUDY PARTICIPATION

There are no alternatives to study participation. Subject may choose not to participate in this research study if they wish.

14. POTENTIAL RISKS

As we anticipate minimal risk from our studies, we doubt any subject will need to be removed or excluded from the study.

There is a very small risk of loss of subject confidentiality. We will protect all subject information to the best

of our ability so this will not happen.

Phase One Study

We believe the risks and discomforts to be small. All patients will be screened for standard contraindications (e.g. implanted device and foreign bodies) for cardiac MRI. If contraindicated, patients will not be enrolled to the study. All participants will be given a full description of the risks associated with MRI scanning as part of informed consent process. Gadolinium contrast, which is required for cardiac MRI, has been associated rarely with the syndrome of nephrogenic systemic fibrosis in patients with moderate to severe kidney diseases. Therefore, moderate or severe kidney disease is one of the exclusion criteria to minimize the potential risk. Small number of patients may experience anxiety or claustrophobia due to the confined space of MRI scan. However, the anxiety or claustrophobia often, if not always, resolves after termination of the scan. We and other investigators have accomplished similar studies without incident.

Phase Two Study

We believe the risks and discomforts to be small. All patients will be screened for standard contraindications (e.g. implanted device and foreign bodies) for cardiac MRI. If contraindicated, patients will not be enrolled to the study. All participants will be given a full description of the risks associated with MRI scanning as part of informed consent process. Gadolinium contrast, which is required for cardiac MRI, has been associated rarely with the syndrome of nephrogenic systemic fibrosis in patients with moderate to severe kidney diseases. Therefore, moderate or severe kidney disease is one of the exclusion criteria to minimize the potential risk. Small number of patients may experience anxiety or claustrophobia due to the confined space of MRI scan. However, the anxiety or claustrophobia often, if not always, resolves after termination of the scan. We and other investigators have accomplished similar studies without incident. Nocturnal oxygen therapy (NOT) and BPAP therapy have both been used in COPD patients in numerous previous research studies without significant reportable risks. NOT and BiLevel therapy will be closely followed and titrated to minimize any discomfort or adverse effects.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

We believe the risks of our research are quite minimal. All recordings will be performed in the closely monitored environment of our research laboratory in the CTF. Emergency equipment and personnel are readily available in the unlikely event of a serious complication.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

We will continue to use our standard methods to protect privacy and confidentiality. All research notebooks are kept in a locked cabinet, with limited access. All computer-based files are kept on a secure network, and backed up to CD-ROM, which are in turn kept in a locked cabinet, such that only the researcher and Principal Investigator have available access. All coded data is transferred in a Secure File Transfer manner or via backed up CD-ROM. Data are all deidentified such that the identity of our study participants could not be discerned by investigators outside of the UCSD.

17. POTENTIAL BENEFITS

There are no direct benefits to participation**.** Society in general may benefit as this study will help achieve a more complete understanding of the upper airway. Only by achieving a more complete understanding of the upper airway dilator muscles can better therapies be developed to treat obstructive sleep apnea.

18. RISK/BENEFIT RATIO

The investigators feel risks associated with these study are outweighed by the benefits. We have greater than 10 years of experience doing this type of research and have never had a serious adverse event.
We anticipate furthering of our knowledge on our understanding of sleep apnea as a result of this research. We will be gathering more information about their sleep and be happy to discuss it with the treating physicians and participants upon request.

19. EXPENSE TO PARTICIPANT

There will be no cost to the subject for participating in this study. All of the tests and procedures that will be done for this research will be paid for by study funds. We will pay for any sleep studies done for research purposes.

Costs for any ongoing or routine medical care subjects would receive apart from this study will be billed to them or to their insurance company in the usual way. The subject will be responsible for any deductibles or co-payments required by your insurer.

20. COMPENSATION FOR PARTICIPATION

To offset transportation costs, parking costs and use of the volunteer's time, subjects will receive $150 for participating in the overnight sleep study and an additional $100 for the completion of the required tests and MRI. In total, subjects can receive $250 for full completion of part I of this research study.

In part 2, there are 4 additional visits. For each additional visit (2, 3, 4 and 5) subjects will be compensated $25.00 for each visit attended. For visit 5, you will receive an additional $100 for the completion of the required tests and MRI.

In total, subjects can receive $450 for full completion of both parts 1 and 2 of this study.

If we were unable to obtain adequate sleep data due to equipment failure or poor signal quality, you will still be compensated $150 for your time and travel. If we ask you to return for a second sleep study in attempt to obtain adequate data and you agree to return, you will be compensated an additional $150 dollars for your time and travel.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Dr. Atul Malhotra is a licensed physician and Principal Investigator of this study. Dr. Malhotra has medical privileges at UCSD and UC Medical Centers to perform sleep studies and treat patients with sleep and pulmonary diseases. Dr. Malhotra will oversee the study and be involved in data analysis and interpretation of the study results.

Dr. Rachel Jen is a visiting scholar from Canada. She is licensed physician (ABIM, FRCPC) and will assist for study recruitment, data analysis, and interpretation of study results. Dr. Rachel Jen will serve as the primary point of contact for this study and will have IRB administrative privileges. Dr. Yanru Li is a licensed physician and will assist with study recruitment, data analysis and interpretation of study results. Dr. Robert Owens is a licensed physician and pulmonologist. He will also assist with the interpretation of study results and data analysis. Josee Beauregard will assist with data analysis and recruitment procedures.

Pam DeYoung and Erik Smales are both certified Registered Polysomnographic Technologists and will perform placement of sleep electrodes (EEG, EOG, EMG, and all respiratory measurements including CPAP as necessary for study protocol) at UCSD Clinical Teaching Facility. Erik Smales and Pam DeYoung will also be responsible

for recruitment, scheduling, data analysis and interpretation of the study results.

All personnel are employed by UCSD and have completed the appropriate CITI training.

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23. FUNDING SUPPORT FOR THIS STUDY

MEDAMSF – to start
RO1 - pending

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

N/A

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

N/A

26. IMPACT ON STAFF

N/A

27. CONFLICT OF INTEREST

The PI and any key personnel associated with this study do not have any financial interests or other "conflicts" related to this study.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

N/A

29. OTHER APPROVALS/REGULATED MATERIALS

N/A

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

N/A