1.a. Full Title: Sleep and Breathing in Patients With Chronic Obstructive Pulmonary Disease

b. Abbreviated Title (Length 26): Sleep and Breathing In COPD

2. Writing Group (list individual with lead responsibility first):
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3. Timeline: Start: on approval/Finish: 1 year

4. Rationale:

   Overall Goals:
   - To assess the prevalence with which lower airways obstruction, Chronic Obstructive Pulmonary Disease (COPD), co-exists with Sleep Apnea/Hypopnea (OSA/H).
   - To assess the prevalence of cardiovascular/cerebrovascular disease in patients with lower airways obstruction and to assess the prevalence of cardiovascular/cerebrovascular disease in patients who have both COPD and OSA/H.

   As is the case with Obstructive Sleep Apnea/Hypopnea (OSA/H), chronic obstructive pulmonary disease (COPD) is associated with poor sleep quality and abnormal oxyhemoglobin desaturation during sleep. Most of these studies sampled relatively small populations, however. Klink et al. examined the prevalence of self-reported sleep disturbances in the Tucson Epidemiologic Study of Obstructive Airways Disease and reported a high prevalence of such disturbances. However, no objective measures of sleep quality, architecture and continuity nor parameters of breathing during sleep were obtained in that study.
Some COPD patients have concomitant OSA/H, termed an “Overlap Syndrome” by Flenley. Chaouat and coworkers recently assessed the prevalence of COPD in a population of middle-aged, predominantly male OSA/H patients who had been referred to a sleep laboratory. Employing a relatively strict definition of COPD (FEV$_1$/FVC $\leq 60\%$), these investigators concluded that at least 10% of OSA/H patients had concomitant COPD reflecting what they considered to be a greater than expected prevalence. Kreiger et al. reported that 7% of OSA/H patients referred to a sleep laboratory had a FEV$_1$/FVC $\leq 65\%$. Conversely, Guilleminault et al. reported that 81% of COPD patients referred to a sleep clinic had notably elevated apnea-hypopnea indices (AHI) ($\geq 30$). It might be postulated that an association between COPD and OSA/H exists due to the presence of mutual risk factors such as tobacco use or the adverse impact of sleep disruption and/or sleep deprivation on upper airway stability during sleep and ventilatory control, respectively. The obvious limitation of the above studies which examined the linkage between COPD and OSA/H however, is that the study populations were highly selected, having been derived from individuals who had been referred to a sleep laboratory for evaluation of sleep-related or potentially sleep-related complaints. There have been no studies examining the degree to which OSA/H and COPD are associated, or co-exist in a community population.

Why is it important to assess the association between COPD and OSA/H? It has been suggested that the presence of COPD confers greater risk of physiologic compromise in OSA/H patients including greater sleep desaturation and greater elevation of pulmonary artery pressure. In the presence of COPD, OSA/H patients experience greater sleep desaturation which is related to both the degree of oxyhemoglobin desaturation during wakefulness, awake arterial carbon dioxide tension and the FEV$_1$.

Several studies suggest that OSA/H is associated with increased cardiovascular and cerebrovascular morbidity and mortality. Further definition of this issue is a goal of the Sleep Heart Health Study (SHHS). In this regard, it is noteworthy that COPD and OSA/H may cause similar physiologic perturbations during sleep that conceptually may contribute to cardiovascular morbidity/mortality. Employing the uric acid:creatinine ratio as a marker of hypoxemia during sleep, Braghiroli and coworkers made similar observations in COPD and OSA/H patients with sleep-associated desaturation. In addition, OSA/H is associated with arousals and enhanced sympathetic nervous system activity and any cardiovascular or cerebrovascular consequences of OSA/H are mediated through these mechanisms. It is plausible that COPD, which is also associated with sleep disruption and desaturation, albeit perhaps in a different pattern than that observed in OSA/H patients, is also associated with a greater than expected prevalence of cardiovascular and cerebrovascular disease. Along these lines, several studies have demonstrated perturbations of autonomic cardiovascular activity in COPD patients. Patakas noted diminished baroreceptor sensitivity in COPD patients compared with age-matched control subjects. Stewart and coworkers reported clearly abnormal cardiovascular autonomic function in at least 35% of COPD patients. Autonomic dysfunction was primarily manifest as heart rate abnormalities in heart rate variability and responses to various physiologic stresses. The magnitude of autonomic dysfunction was correlated with P$_{O_2}$. The authors concluded that the autonomic dysfunction was related to the impact of hypoxemia on the endoneural capillary basement membrane resulting in endoneural hypoxemia. Sleep studies were not performed and the potential impact of
nocturnal hypoxemia was not explored in this study. Notably, autonomic
dysfunction was noted in the study group with minimal awake hypoxemia (mean P_{a}O_{2};
71.3 mmHg) raising the possibility that the adverse impact was mediated through
desaturation. Miyamoto and coworkers observed that COPD patients had
exaggerated heart rate augmentation in the presence of hypoxia compared with
normal control subjects. The degree of augmentation was weakly correlated with
parameters of pulmonary function and it was hypothesized that the underlying
mechanism is enhanced sympathetic activity in the COPD patients.

Both OSA/H and COPD impact on the cardiovascular system in terms of predisposing
to sleep ischemia and dysrhythmias. Shepard et al. observed increased
ventricular irritability in conjunction with more severe desaturation in COPD
patients. Similarly, Flick et al. noted a particular predisposition of some COPD
patients to have premature ventricular contractions during sleep. Along these
lines, OSA/H patients also may be predisposed to nocturnal arrhythmias. In
addition, both COPD and OSA/H patients may be specifically susceptible to cardiac
ischemia during sleep, although it is possible that the COPD patients reported
but Tirlapur had co-existent OSA/H.

Thus, a physiologically abnormal environment may exist in both COPD and OSA/H
patients which promotes cardiovascular and cerebrovascular morbidity and
mortality. As noted previously, the published literature suggests increased
cardiovascular mortality in OSA/H patients. In this light, it is of interest
that in a population of 169 COPD patients without OSA/H, Fletcher et al. observed
a decreased survival in those patients with nocturnal desaturation compared with
non-desaturators. The cause of death was not reported, however.

In as much as OSA/H and COPD are each associated with sleep desaturation,
disrupted sleep and possibly increased cardiovascular autonomic balance, it is
plausible that there is a particularly high prevalence of cardiovascular and
cerebrovascular disease in patients with the "Overlap Syndrome". This remains
to be evaluated, however.

5. Main Hypothesis:

Question #1: Can non-apneic (Respiratory Disturbance Index ≥ 5)
oxyhemoglobin desaturation be predicted by the severity of
COPD measured by spirometry?

Question #2: Can sleep quality, architecture and continuity be predicted by
the severity of COPD measured by spirometry, independent of
OSA/H?

Hypothesis #1: Patients with COPD have worse sleep quality and continuity than
individuals without COPD.

a. Patients with COPD and oxyhemoglobin desaturation during sleep have
worse sleep quality and continuity than COPD patients without sleep
desaturation.

b. Spirometry is an independent predictor of sleep quality and continuity
(independent of awake oxyhemoglobin saturation-SaO2, RDI depending on
definition, age, and weight)

c. There is a greater prevalence of perceived sleepiness in patients with
COPD without OSA/H compared with normal individuals and a greater
prevalence of perceived sleepiness in patients with COPD and OSA/H than
in those with COPD or OSA/H alone.

Question #3: What is the prevalence with which COPD and OSA/H occur concomitantly in the community?

Question #4: Does the presence of COPD predict the presence of OSA/H?

Hypothesis #2 (null): The prevalence of OSA/H is not increased in patients with COPD

Question #5: Is there a greater prevalence of cardiovascular and cerebrovascular disease in COPD patients than individuals without COPD or OSA/H?

Question #6: Do patients with COPD and oxyhemoglobin desaturation during sleep have a greater prevalence of cardiovascular and cerebrovascular disease than COPD patients without sleep desaturation?

Question #7: Is there a greater prevalence of cardiovascular and cerebrovascular disease in patients with COPD and OSA/H than in those with COPD or OSA/H alone?

Question #8: Is the prevalence of sleep-associated dysrhythmias greater in patients with COPD alone than in normal individuals and is the prevalence of sleep-associated dysrhythmias greater in patients with COPD and OSA/H than in those with COPD or OSA/H alone?

Hypothesis #3: Patients with COPD have a greater prevalence of cardiovascular and cerebrovascular disease than individuals without COPD or OSA/H.
   a. Patients with COPD and oxyhemoglobin desaturation during sleep have a greater prevalence of cardiovascular and cerebrovascular disease than COPD patients without sleep desaturation.
   b. There is a greater prevalence of cardiovascular and cerebrovascular disease in patients with OSA/H than in patients with COPD.
      i. differences are independently predicted by sleep desaturation and arousal frequency
   c. There is a greater prevalence of cardiovascular and cerebrovascular disease in patients with COPD and OSA/H than in those with COPD or OSA/H alone.
      i. differences are independently predicted by sleep desaturation and arousal frequency

Hypothesis #4: There is a greater prevalence of sleep-associated dysrhythmias in patients with COPD than individuals without COPD.
   a. The prevalence of sleep-associated dysrhythmias in patients with COPD alone is greater than in normal individuals the prevalence of sleep-associated dysrhythmias is greater in patients with COPD and OSA/H than in those with COPD or OSA/H alone.
   b. Spirometry, awake and sleep SaO2 are independent predictors of sleep-associated dysrhythmias.

6. Data (variables, time window, source, inclusions/exclusions):
   The study population will consist of SHHS participants who have completed a Health Interview Form and pulmonary function tests within the last 3 years. It is not believed that the full anticipated data set of 6000 participants is required for this study (see power calculation, below).
   a) The following variables will be included in the analyses:
      • age
• gender
• weight/height
• race, ethnicity
• tobacco habits
• sleep habits
• self-reported medical diagnoses
• cardiovascular and cerebrovascular diseases
• diagnosis of COPD (chronic bronchitis, emphysema, asthma)
• depression score
• sleep complaints
• alcohol consumption
• Medications (especially bronchodilators, hypnotics, psychotropic agents,
  anti-hypertensive agents and anti-anginal agents)
• awake $S_O_2$
• pulmonary function test results (spirometry: FEV$_1$, FVC, FEV$_1$/FVC) adjusted
  for age, sex and height.

b) The following SHHS variables will be included in the analyses:
• Apnea+Hypopnea Index (although analyses may employ other parameters of
  sleep-disordered breathing; non-REM specific AHI and REM specific AHI)
• Oxyhemoglobin Desaturation Index ($ODI_2$, $ODI_3$)
• Time distribution (as percent of total sleep time) of oxyhemoglobin
  saturation
• Sleep latency
• Total sleep time
• Sleep efficiency
• Arousal Index
• Time in each sleep stage (as percent of Sleep Period Time)
• Presence and nature of dysrhythmias and relationship to sleep stage