Propranolol for Sleep Apnea Treatment (PROSAT)

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PROPRANOLOL FOR SLEEP APNEA THERAPY (PROSAT)

STATISTICAL PLAN

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Developed by:

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Background:

20 million adults in the United States and >100 million adults worldwide have OSA, and the prevalence continues to rise with obesity. These figures are especially alarming as OSA is associated with cardiovascular disease and mortality. However, mechanisms linking OSA to these outcomes are unclear. As a result of this knowledge gap, fundamental questions such as what features of OSA are most harmful, and which patients can safely decline treatment, cannot be answered. Moreover, therapies for OSA such as CPAP are poorly tolerated, leaving non-adherent patients susceptible to CVD. We have observed that OSA acutely elevates nocturnal heart rate, morning blood pressure, and morning augmentation index (AIX)[1]. These short-term changes may foster progression of cardiovascular disease if they recur on a chronic basis. In other contexts, these cardiovascular changes are induced by sympathetic nervous system activation. Therefore, we hypothesize that catecholamine release during sleep leads to increased heart rate, blood pressure, AIX, and altered metabolism. In this project we will examine whether OSA-related cardiometabolic changes during sleep can be prevented by beta blockade.

Design: Double-blind, crossover RCT of Propranolol LA vs. Placebo taken before sleep in patients with moderate-severe OSA. Participants will be CPAP-adherent patients who will temporarily discontinue CPAP for 3 nights prior to each visit, approximately 1 week apart. During sleep we will collect a full sleep study (oximetry, sleep staging, respiratory flow, muscle movements), IV blood samples (every 30 min). In the morning following each study, participants will undergo vascular assessment (endoPAT testing).

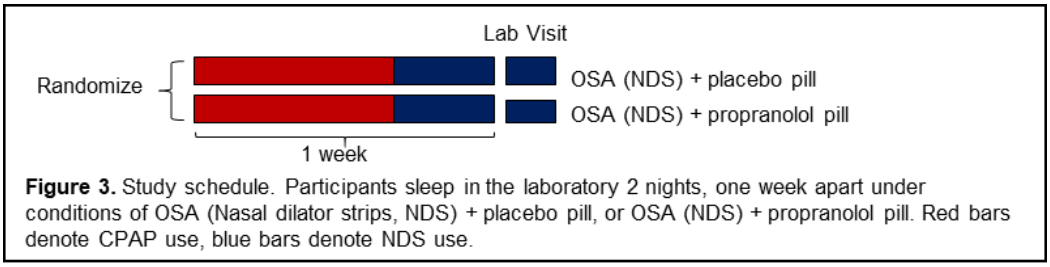
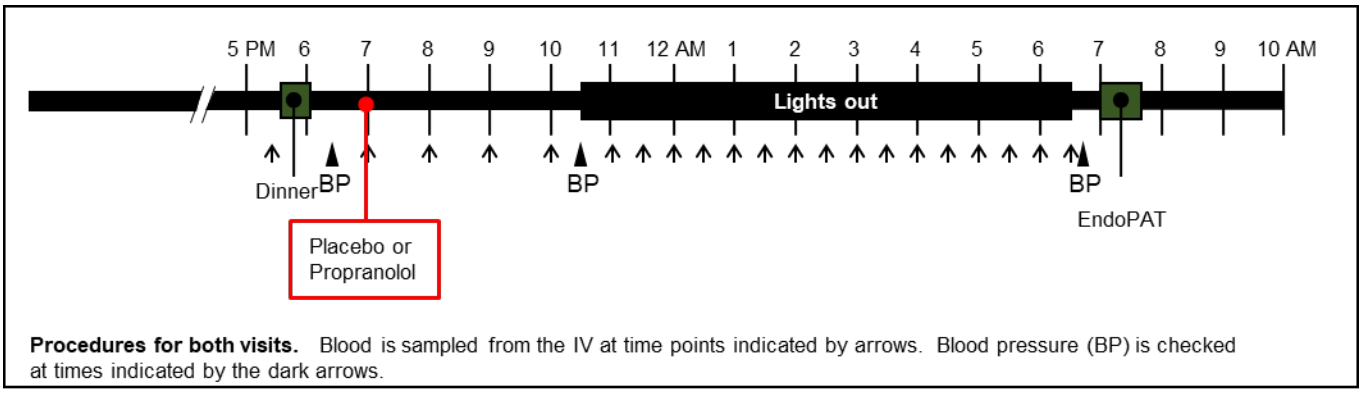


Figure 3. Study schedule. Participants sleep in the laboratory 2 nights, one week apart under conditions of OSA (Nasal dilator strips, NDS) + placebo pill, or OSA (NDS) + propranolol pill. Red bars denote CPAP use, blue bars denote NDS use.



Procedures for both visits. Blood is sampled from the IV at time points indicated by arrows. Blood pressure (BP) is checked at times indicated by the dark arrows.

Sample size: In a preliminary study (n=6), Median individual heart rate during sleep ± (SD) was 62.2 (9.2) with [OSA+placebo] and this decreased by 6.7 BPM with [OSA+propranolol]. To detect a 10% difference (reduction of 6.2 beats/min) at a power of 80% at a significance threshold of 0.05, using a one-tailed comparison, yields a sample size of 16 participants. Since we have already enrolled 5 subjects, we require 11 additional subjects. Assuming 20% dropout, we will enroll 14 additional subjects, a total of 19 participants.

Primary outcome: Median of continuously measured heart rate during sleep.

Secondary outcomes:

- augmentation index (normalized to 75 beats/min),
- heart rate variability metrics (HR standard deviation, min/max, 5th or 95th percentile)
- OSA severity (AHI, oximetry, event duration)
- sleep architecture (percent of each sleep stage during the night)
- Blood pressure
- metabolism (FFA, glucose, insulin).

Blinding:

As this is a double-blind study, above metrics will be calculated for each visit with only knowledge of visit number and not drug/placebo assignment. After these parameters have been derived, the research pharmacy will un-blind the biostatistician (Perin) and PI (Jun) to drug arm assignment to apply appropriate statistical tests, as described below.

Analysis:

For the primary analysis, we will derive summary metrics per night, per participant (i.e. median HR per night). Median heart rate per night will be compared between drug and placebo nights in a paired framework using paired student's T tests. Similar methods will be used to compare secondary outcomes. Some metrics will require additional derivation. For example, heart rate variation will be expressed as coefficients of variation, min/max and lower (5th) and upper (95th) percentiles, and visualized with Poincare plots as performed by collaborators at Johns Hopkins [2].

Exploratory Analyses:

Since several outcomes involve time series data (e.g. heart rate, oxygen level during sleep, apnea-hyponea index) we will also evaluate trajectories of these metrics over time, and to detect potential drug x time interactions (i.e. the within night trajectories may vary depending on whether propranolol was received). For example, propranolol may have progressive effects over the course of the night as the drug is absorbed. For these time series analyses, we will reduce continuous metrics into 30-minute average bins (other bin sizes may also be trialed depending on clinically relevant time domains of the outcome). Mixed effects linear models will be used to compare these parameters using drug as the fixed factor, with a random effect for each subject. We will additionally incorporate time in the analysis using mixed effects models with time as a covariate and including a drug*time interaction. Random slopes and intercepts will be used in these regressions.

We anticipate that propranolol will significantly decease heart rate. Propranolol may have effects on other outcomes (such as blood pressure or augmentation index), mediated by heart rate. We will examine these potential associations in linear regression (for example, change in HR versus change in blood pressure).

REFERENCES

1. Chopra, S. *et al.* Obstructive Sleep Apnea Dynamically Increases Nocturnal Plasma Free Fatty Acids, Glucose, and Cortisol During Sleep. *J. Clin. Endocrinol. Metab.* **102**, 3172–3181 (2017).
2. Kim, L. J., Pho, H., Pham, L. V. & Polotsky, V. Y. Isocapnic CO2 administration stabilizes breathing and eliminates apneas during sleep in obese mice exposed to hypoxia. *Sleep* zsac243 (2022) doi:10.1093/sleep/zsac243.