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Permalink

<https://escholarship.org/uc/item/5n11w1qw>

Journal

Sleep and Breathing, 30(1)

ISSN

1520-9512

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Publication Date

2026-03-01

DOI

10.1007/s11325-026-03597-z

Peer reviewed



Metabolic assessments of neurostimulation therapy to reduce apnea (MANTRA) trial: rationale and methods

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Received: 7 September 2025 / Revised: 9 January 2026 / Accepted: 23 January 2026 / Published online: 16 February 2026
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Abstract

Purpose To investigate the effects of hypoglossal nerve stimulation (HGNS) therapy on energy balance and insulin resistance among patients stabilized on HGNS.

Methods In this randomized, within-subject crossover trial, we compare energy balance and insulin resistance during active HGNS (“HGNS-on”) versus HGNS withdrawal (“HGNS-off”) among 30 patients with OSA who have been stabilized on HGNS for ≥ 3 months. Participants will undergo between 2–4 weeks of each study phase (HGNS-on and HGNS-off), with the duration of HGNS-on and HGNS-off standardized within participants. Between the two study phases (HGNS-on and HGNS-off), patients resume HGNS for 1 week. At the end of each study phase, participants undergo fasting anthropometric measurements, blood sample collection, and home sleep testing. A subset of participants undergo additional assessments of energy expenditure (via doubly labeled water technique) and energy intake.

Results The primary outcome is energy balance, as calculated from the difference between energy expenditure and energy intake. The secondary outcome is insulin resistance, as assessed by the homeostatic model assessment for insulin resistance.

Conclusion There is a dearth of mechanistic data examining the metabolic effects of HGNS. We present methods of the Metabolic Assessments of Neurostimulation Therapy to Reduce Apnea (MANTRA) trial, the first randomized crossover study designed to examine the metabolic effects of HGNS.

Keywords Hypoglossal nerve stimulation · Obstructive sleep apnea · Metabolic health · Cardiometabolic outcomes · Sleep apnea surgery · Upper airway stimulation · Energy balance · Energy expenditure · Insulin resistance · Inflammation

Meetings: Presented as an oral presentation at the International Surgical Sleep Society 2025 Annual Meeting, Indianapolis, Indiana, October 10, 2025.

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Introduction

Obstructive sleep apnea (OSA) is a prevalent disorder with major cardiometabolic sequelae [1]. Continuous positive airway pressure (CPAP) is first-line therapy for adults with moderate or severe OSA and can provide significant relief of symptoms. Observational studies have indicated potential improvements in cardiometabolic outcomes with CPAP [1, 2], but randomized clinical trials (RCTs) have not substantiated these observations [3–5]. Low CPAP adherence (e.g. 2.8–5.0 h/day [3, 4]) and exclusion of excessively sleepy patients may have limited the ability of these RCTs to detect potentially beneficial effects of CPAP therapy [6]. However, an alternative is that CPAP may have minimal or even possibly adverse impacts on certain cardiometabolic measures [7].

A growing body of literature suggests potential adverse cardiometabolic effects of CPAP therapy. For example, modest increases in weight and BMI have been observed in patients with OSA after 3–6 months of CPAP [8]. The underlying mechanisms of CPAP-associated weight gain are poorly understood but may be influenced by comorbid dysglycemia [8], cardiovascular disease (CVD) [8], dietary intake, or poor lifestyle choices/behaviors. CPAP may also affect the heart atria and lead to significant reductions in atrial natriuretic peptide that may drive fluid retention [9, 10]. Recent studies also suggest that CPAP may promote a pro-inflammatory state due to excessive alveolar distension [7, 11], which may counteract the expected reduction in CVD risk of OSA reduction even with adequate adherence. Importantly, other OSA therapies are available that are not known to increase inflammation and may have divergent effects on cardiometabolic health.

Hypoglossal nerve stimulation (HGNS) is a surgical OSA therapy that was approved by the US Federal Drug Administration (FDA) in 2014 for adults with a body mass index (BMI) ≤ 32 kg/m² and an apnea-hypopnea index (AHI) of 15–65 who cannot tolerate CPAP. HGNS has been increasingly adopted and has demonstrated long-term effectiveness and OSA symptom relief [1]. Yet, the cardiometabolic effects of HGNS are unknown. In June 2023, the FDA approved an indication expansion to increase the BMI upper limit recommended for HGNS to 40 kg/m². Given that the target population for HGNS has been expanded to include individuals with class II obesity (BMI ≥ 35 to 40 kg/m²) who are at higher cardiometabolic risk, there is a pressing need to elucidate the cardiometabolic effects of HGNS.

Energy balance, insulin resistance, and inflammation play pivotal roles in the mechanisms underlying metabolic dysfunction and cardiometabolic risk [12], but there is a dearth of literature examining these measures in HGNS patients [13]. Energy balance is the difference between

energy expenditure and energy intake, with positive energy balance contributing to weight gain and obesity [12]. Insulin resistance (a state of decreased cellular response to insulin contributing to elevated glucose levels and compensatory hyperinsulinemia) is another driver of metabolic dysfunction [14]. Several studies have demonstrated an association between insulin resistance and OSA [1, 2], but studies with CPAP have shown varying effects on insulin resistance in OSA [3, 4, 6, 15]. Given HGNS's distinct mechanism of action compared to CPAP, investigation of its impact on energy balance and insulin resistance is warranted.

In this study, we recruit patients with OSA who have been stabilized on HGNS for ≥ 3 months and conduct a randomized, crossover trial to compare energy balance and insulin resistance during 2–4 weeks of active HGNS ("HGNS-on") vs HGNS withdrawal ("HGNS-off"). We aim to test the impact of HGNS on: 1) energy balance via assessments of energy expenditure and energy intake and 2) insulin resistance. We hypothesize that HGNS-on is associated with greater free-living energy expenditure, no difference in energy intake, and lesser insulin resistance as compared to HGNS-off.

Methods

The Metabolic Assessments of Neurostimulation Therapy to Reduce Apnea (MANTRA) study is an ongoing randomized crossover trial involving 2–4 weeks of active HGNS ("HGNS-on") and 2–4 weeks of HGNS withdrawal ("HGNS-off"). Between these study phases (HGNS-on and HGNS-off), participants undergo a one-week return to baseline conditions with active HGNS therapy (i.e. wash-out period). Participants have the option of participating in both Aims 1 and 2 or Aim 2 only. Participants who choose only Aim 2 are provided the option to undergo as little as 2 weeks of the study phases to improve recruitment, given that untreated OSA during HGNS-off may be disruptive. Study participants undergo outcome assessments at the end of each study phase: 1) energy expenditure via doubly labeled water (DLW) technique and actigraphy, 2) energy intake via 3-day food records with the Automated Self-Administered 24-hour Dietary Assessment Tool (ASA24) [16], 3) anthropometric measures, and 4) fasting glucose and insulin to obtain homeostatic model assessment for insulin resistance (HOMA-IR). This study is approved by Columbia University's Institutional Review Board (AAAU9827).

Study population and inclusion criteria

Participants treated with HGNS are recruited from the NewYork-Presbyterian Hospital HGNS patient database

and the broader New York City metropolitan area. Inclusion criteria are as follows: 1) English or Spanish-speaking adults (age ≥ 18 years) who are able to give informed consent, 2) have undergone HGNS with a subsequent $\geq 50\%$ reduction in AHI to a post-operative AHI < 20 with therapy, 3) have adhered to HGNS for ≥ 3 months for ≥ 20 h/week, and 4) have previously undergone at least a one-month period without OSA therapy prior to HGNS activation (and thus have previously tolerated a one-month period of untreated OSA consistent with HGNS-off study conditions). Individuals are excluded from the study if they: 1) are on anti-obesity medications, or insulin without stabilized dosages; 2) chronically use hypnotics, anti-psychotic medications, stimulants, benzodiazepines, opioids, or sleep aids; 3) are pregnant; 4) are shift workers, heavy machinery operators, or commercial drivers; 5) have severe cardiopulmonary, renal (e.g., require dialysis), or neurodegenerative disease; 6) cannot abstain from driving during the study *and* have a history of Epworth Sleepiness Scale score ≥ 20 or motor vehicle accidents/near-miss incidents.

Sample size and power calculations

We plan total enrollment of 30 participants based on sample size calculations below, with Aim 1 study procedures conducted in a subset of our total sample.

Aim 1

To our knowledge, there is no existing literature on HGNS and energy expenditure (primary outcome). In a pilot study of 3 participants randomized to active vs sham CPAP, active CPAP was associated with average 24-hour energy expenditure that was greater (2705 ± 217 kilocalories per day (kcal/d) with sham CPAP vs. 2970 ± 254 kcal/d with active CPAP) [17]. Using 265 kcal/d as a clinically significant and expected change in energy expenditure with HGNS withdrawal, and a standard deviation (SD) of 217 kcal/d, a sample size of 8 would sufficiently power the study with $\alpha=0.05$ and 80% power. We will target enrollment of $n=12$.

Aim 2

In a study of 44 non-HGNS OSA surgery patients with 50% surgical response rate, Wang et al. noted a significant change in HOMA-IR of -0.84 (95% confidence interval, $[-1.55, -0.13]$, $p=0.009$) [18]. Using 0.84 as a clinically significant and expected reduction in HOMA-IR and SD of 1.35 per Wang et al., $n=23$ would sufficiently power the study with $\alpha=0.05$ and 80% power. We plan to recruit 30 participants to account for a $\sim 20\%$ attrition rate due to inability to tolerate

HGNS-off, unanticipated study visit absences, or participant deviations from study protocols.

Overview of study design

Upon study initiation, participants are randomized, stratified by sex and BMI < 30 or ≥ 30 kg/m², to either 2–4 weeks of HGNS withdrawal (HGNS-off) or HGNS therapy (HGNS-on) for the first phase of the study (“Phase 1”). They are informed of randomization results 72 hours prior to initiation. Between phases, a 1-week washout period (during which participants return to their baseline conditions of HGNS-on) allows the participants who were randomized to HGNS-off first to reacclimate to therapy [19, 20] and ensures the same pre-intervention conditions for both phases. A 1-week HGNS-off washout was considered, but not selected because prolonged HGNS-off intervals may increase participation risk due to periods of untreated OSA and reduce recruitment feasibility. Prior trials have also demonstrated that OSA severity after HGNS withdrawal returned to pre-implant levels within one week [19]. After washout, participants begin Phase 2, during which those who were randomized to HGNS-off first transition to HGNS-on, and vice versa.

For all participants, endpoint visits occur at the end of each phase. One week prior to each endpoint visit, participants are provided with a home sleep test (HST). At the endpoint visit, anthropometric measures and blood samples are collected. Visits occur in the morning after an overnight fast, and participants abstain from caffeine and exercise for > 24 hours prior to each visit. Data from participants’ HGNS remotes are reviewed for HGNS on/off adherence.

For the subset of Aim 1 participants, doubly labeled water (DLW) is administered at two additional dosing visits at the midpoint of phases 1 and 2 with urine samples collected at home and study visits (details below). During dosing visits, anthropometric measurements and blood samples are also collected. Participants then complete the ASA24 food intake logs [16], actigraphy, and urine collection at home. Example study schedules are shown in Figures 1 and 2.

Protocol details

Total daily energy expenditure by DLW

We will employ established institutional DLW methods [21] to measure free-living energy expenditure. Briefly, energy expenditure is measured over 2 weeks per study phase starting at the midpoint of each phase. Prior to DLW dosing, a baseline urine sample is obtained to determine background enrichments of ²H and ¹⁸O. Urine samples are obtained

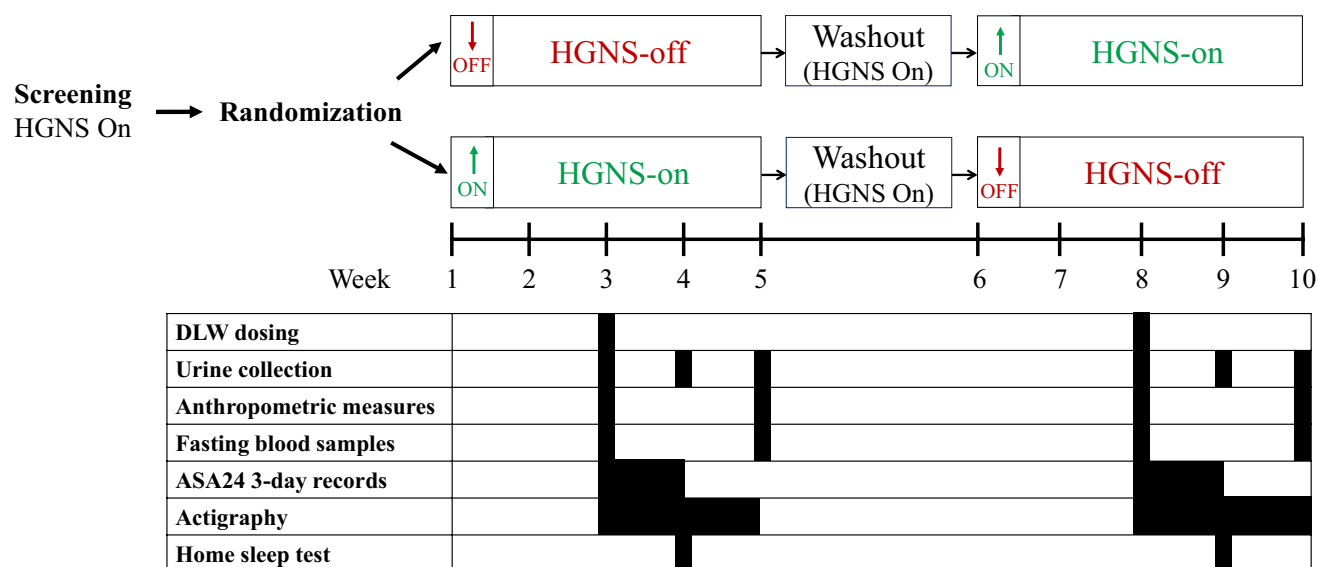


Fig. 1 Example schedule for participants in Aim 1 and Aim 2

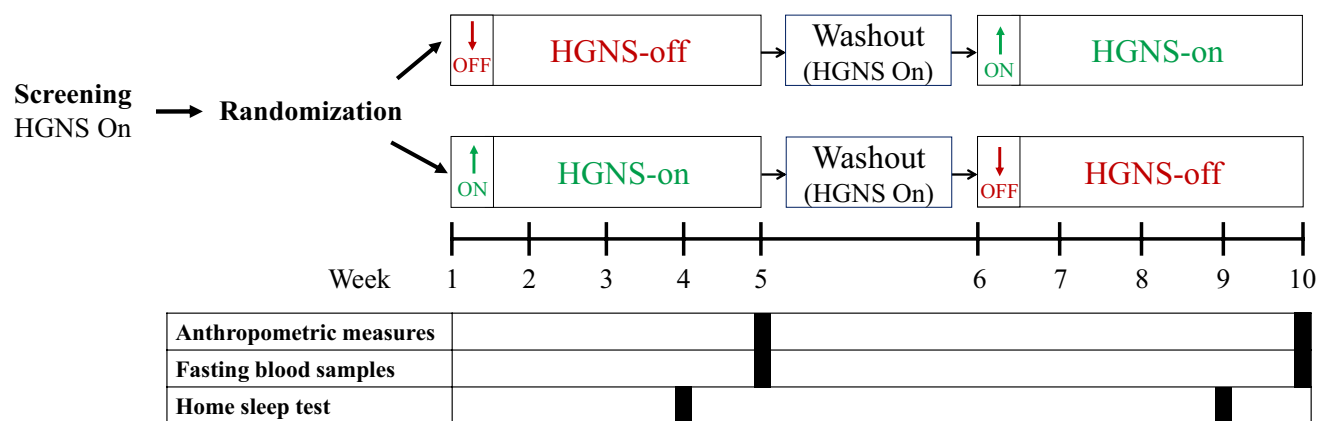


Fig. 2 Example schedule for participants in Aim 2 only

4 and 5 hours after dosing. Participants then complete a 1-week at-home urine collection (second morning void) and store the sample in their freezer until endpoint visits.

At the end of phases 1 and 2, participants return to our center for endpoint visits. Two urine samples are collected one hour apart, and sample aliquots are frozen at -20°C and shipped on dry ice for analysis. Respiratory quotient, fat, and carbohydrate oxidation rates will be calculated [21] from O_2 consumption and CO_2 excretion data using a formula by Lusk [22].

Physical activity and sleep duration by actigraphy

We measure physical activity level during the last 2 weeks of each phase (after DLW dosing). We provide each participant with an Actigraph GT3X (ActiLife LLC, Pensacola, FL) device to wear at the waist (the validated placement for physical activity measures) from wake time to bedtime,

removing the device only for bathing/showering. Using the ActiLife software Freedson Adult settings, we determine total activity counts, which have been associated with cardiometabolic biomarkers [23]. At bedtime, participants move the actigraph to their non-dominant wrist until wake time. Participants also keep a sleep diary to record in-bed/out-of-bed times and sleep disturbances (awakenings, unusual activity, etc). Sleep is scored using the Cole-Kripke algorithm [24].

Dietary intake via ASA24

The ASA24 is a research-grade, validated online tool developed by the National Cancer Institute that enables automatically coded food diaries [16]. Participants complete dietary records for three 24-hour recall periods during the second half of phases 1 and 2 on Tuesday, Thursday, and Saturday [16]. Healthy Eating Index scores are calculated per

National Cancer Institute protocol. Daily energy intake and macronutrient intakes are provided by the ASA24 system on the US Department of Agriculture FoodCentral database. Intake values are averaged across all measurement days for each phase.

Body composition measures

At each study visit, participants are measured without shoes while wearing a hospital gown. Measurements are taken in duplicate for: 1) weight from a standard beam scale to the nearest 0.1 kg, 2) height from a stadiometer to the nearest 0.1 cm, and 3) waist circumference directly above the iliac crest to the nearest 0.1 cm using a Gulick II tape measure.

Fasting blood samples

Fasting blood samples are collected at each study visit. Samples are processed and aliquots are frozen at -80°C until analysis. COBAS Integra 400 Plus (Roche Diagnostics, Indianapolis, IN) chemistry analyzer is used for glucose analysis. Enzyme-linked immunosorbent assay is used for insulin (EMD Millipore Corporation, Billerica, MA). HOMA-IR is calculated per the formula [25], $[\text{fasting plasma glucose (mmol/L)}] \times [\text{fasting plasma insulin } (\mu\text{mol/L})] / 22.5$.

Home sleep testing

Participants are provided with a Zmachine Synergy HST, a validated HST with 9 channels (including EEG-based sleep staging, respiratory airflow, snore, respiratory effort, 3-axis body position, pulse oximetry; General Sleep Corporation, Cleveland, OH). Participants conduct the HST the week before each endpoint visit. Upon data download, the participant is asked to repeat the test immediately if data are not viable. The study PI interprets all sleep studies while blinded from participants' HGNS on/off status. Historical (pre-study) polysomnography data obtained as part of clinical care are summarized descriptively for cohort characterization whereas HST study metrics are used as contemporaneous measures for phase-specific OSA.

Participant non-adherence to study protocols

If participants deviate from assigned HGNS on/off conditions, our study team discusses the deviations with the participant. The study PI determines whether to recommend study termination or offer participants the option to restart the applicable study phase after 1 week of washout (HGNS-on). If participants were able to complete phase 1 for at least

2 weeks but feel unable to complete the remainder, they are disqualified from Aim 1 but are allowed to complete Aim 2.

Results

Statistical analysis

We will present results for all participants accrued and completers. Analysis will be performed using general linear mixed models with subject number as random effect, visit (baseline/endpoint), condition (HGNS-on/HGNS-off), and visit $\times$ condition as variables in the models. Study phase (1 or 2) will be included to test for order effects and removed from models if not significant. We will also include sex and difference in AHI between study phases sequentially as covariates. Only covariates that are significant will be retained in final models. Sex $\times$ condition and BMI $\times$ condition interactions will also be tested, but given our a priori plan to evaluate sex differences, models will be analyzed separately by sex and BMI regardless of the significance of the interaction term.

Discussion

HGNS has become an increasingly adopted CPAP alternative, but there is a dearth of mechanistic studies examining the cardiometabolic outcomes of HGNS. While existing studies on CPAP are relevant, HGNS may produce divergent outcomes due to its differing mechanism of action, high therapy adherence, and possible lack of pro-inflammatory changes associated with CPAP [7, 11]. Our study is the first to examine the metabolic outcomes of HGNS using a within-subject randomized crossover design. The results bear important implications for a patient population at high risk for cardiometabolic disease. If our hypotheses are supported, our work may provide support for considering HGNS in patients with OSA at higher cardiometabolic risk. Our findings would also provide useful information for patients seeking HGNS to improve their health outcomes, which is the most common patient-reported treatment goal in seeking OSA surgery [26].

We anticipate limitations of our study. The necessary HGNS-off period may lead to potential selection bias, as patients who have experienced substantial improvements with HGNS may be unwilling to suspend therapy for even these short periods of time. This will bias results against a treatment effect of HGNS (and towards the null hypothesis of no effect). To address this potential bias and improve feasibility and participant adherence, we allowed

the duration of HGNS-on and HGNS-off phases to be as short as 2 weeks, with equal study phase durations within each participant. To account for this, study phase duration will be modeled as a covariate in our statistical analysis. We also acknowledge the study period is a relatively short time frame, though changes in various cardiometabolic measures (e.g. blood pressure, heart rate, and endothelial function) have been observed after 2 weeks of CPAP withdrawal [27, 28]. Although longer durations may be required to observe more durable effects, our study is intended to detect early changes in metabolic markers, and the results will inform future studies and effect size estimates if a signal is observed. We will also exclude participants who have not achieved surgical success (based on Sher₂₀ criteria) with HGNS to optimize for potential effect size given the short time frame of our study phases. Although HGNS literature suggests that OSA severity returns to baseline within one week of HGNS withdrawal, the washout kinetics of any potential cardiometabolic effects of HGNS are unknown. We thus acknowledge the possibility of any residual carryover to attenuate observed between-condition differences. However, understanding whether short-term HGNS withdrawal has cardiometabolic effects is a central knowledge gap that this trial is designed to address. Lastly, our primary source of recruitment from an academic tertiary care center and the exclusion of patients on dialysis, insulin, or weight loss medications may also limit generalizability. Collectively, these factors may result in a study cohort that does not fully capture the heterogeneity of the broader HGNS population.

Notably, our study also offers several strengths. Our study employs a rigorous approach in assessing multiple mechanistic underpinnings of metabolic dysfunction, including application of the gold-standard methodology for assessing energy expenditure in free-living conditions via DLW. Prior studies in OSA have used whole-room indirect calorimetry measurements of energy expenditure (necessitating participant restriction to a metabolic chamber), but DLW has not yet been employed in prior OSA studies to our knowledge. Our study also leverages the on/off functionality of HGNS to assess its effects using a randomized, within-subject design, a gold standard for mechanistic clinical trials. Fasting blood samples collected in our study will serve as the foundation for a biospecimen repository in the HGNS population, enabling future mechanistic investigations. Lastly, this trial will be the first to investigate a sustained period of complete HGNS withdrawal lasting one month, whereas prior studies have examined subtherapeutic HGNS up to 4 weeks [29] or withdrawal of a single week [19, 20, 30]. Taken together, the results from this trial will be valuable in informing future HGNS study design and providing novel data regarding the cardiometabolic effects of HGNS.

Conclusion

The MANTRA trial is the first study designed to examine the metabolic effects of HGNS through a randomized, within-subject crossover trial design. The results bear important implications for a patient population vulnerable to high cardiometabolic risk. Our work may lay the foundation for future studies of additional cardiometabolic outcomes of HGNS and provide valuable insights for future HGNS study design.

Authors' contribution Yi Cai: study conception and design, acquisition of data, analysis and interpretation of data, manuscript writing. Allison Lin: acquisition of data, manuscript writing. Rachel B. Kutler: acquisition of data. Jesus A. Lopez-Peña: acquisition of data. Maria V. Suurna: acquisition of data, manuscript editing. Ashutosh Kacker: acquisition of data, manuscript editing. Bin Cheng: study design, manuscript editing. Eric J Kezirian: study design, manuscript editing. Justin Golub: study design, manuscript editing. Sanja Jelic: study design, manuscript editing. Marie-Pierre St-Onge: study conception and design, manuscript writing.

Funding This work is funded by the American Academy of Sleep Medicine Foundation. Dr. Cai reports consulting fees from Aerin Medical and additional funding from the Triological Society, American Heart Association, and Columbia Technology Ventures. Dr. Suurna is a consultant for Inspire Medical. Dr. Kezirian is supported by NIH R01HL160993. Dr. St-Onge is supported by NIH R35HL155670. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data availability The data gathered for this study are not openly available to maintain patient privacy. De-identified data will be made available to other investigators upon reasonable request.

Declarations

Ethical standards This study has been approved by the Columbia University Institutional Review Board (IRB # AAAU9827) and is therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent All persons gave their informed consent prior to inclusion as stated in the methods.

Competing interests The authors declare no conflicts of interest.

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