Nature and Science of Sleep

Elevate Series

Open Access Full Text Article

ORIGINAL RESEARCH

Exploring the Relationship Between Sleep Apnea, Myocardial Infarct Size, and Coronary Collaterals in Acute Myocardial Infarction: A Multidisciplinary Study

Vaishnavi Kundel[1], Kavya Devarakonda[1], Samira Khan[1], Mayte Suarez-Farinas[1], Oren Cohen[1], Carlos Santos-Gallego[1], Mark A Menegus[2], Annapoorna Kini[1], Yuliya Vengrenyuk[1], Naotaka Okamoto[1], Hiroshi Ueda[1], Umesh Gidwani[1], Jorge R Kizer[3], Susan Redline[4], Robert Kaplan[2,5], Neomi Shah[1]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Albert Einstein College of Medicine, Bronx, NY, USA; [3]Cardiology Section, San Francisco Veterans Affairs Health Care System and Departments of Medicine, Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA, USA; [4]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [5]Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Correspondence: Vaishnavi Kundel, Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Icahn School of Medicine at Mount Sinai, One Gustave L Levy Place, Box 1232, New York, NY, 10029, USA, Tel +1-212-241-1967, Email Vaishnavi.kundel@mssm.edu

Purpose: We designed a study investigating the cardioprotective role of sleep apnea (SA) in patients with acute myocardial infarction (AMI), focusing on its association with infarct size and coronary collateral circulation.

Methods: We recruited adults with AMI, who underwent Level-III SA testing during hospitalization. Delayed-enhancement cardiac magnetic resonance (CMR) imaging was performed to quantify AMI size (percent-infarcted myocardium). Rentrop Score quantified coronary collateralization (scores 0–3, higher scores indicating augmented collaterals). Group differences in Rentrop grade and infarct size were compared using the Wilcoxon Rank-Sum test and Fisher's Exact test as appropriate, with a significance threshold set at $p < 0.05$.

Results: Among 33 adults, mean age was 54.4±11.5 and mean BMI was 28.4±5.9. 8 patients (24%) had no SA, and 25 (76%) had SA (mild n=10, moderate n=8, severe n=7). 66% (n=22) underwent CMR, and all patients had Rentrop scores. Median infarct size in the no-SA group was 22% versus 28% in the SA group (p=0.79). While we did not find statistically significant differences, moderate SA had a trend toward a smaller infarct size (median 15.5%; IQR 9.23) compared to the other groups (no SA [22.0%; 16.8,31.8], mild SA [27%; 23.8,32.5], and severe SA [34%; 31.53], p=0.12). A higher proportion of moderate SA patients had a Rentrop grade >0, with a trend toward significance (moderate SA versus other groups: 62.5% versus 28%, p=0.08).

Conclusion: Our study did not find statistically significant differences in cardiac infarct size and the presence of coronary collaterals by sleep apnea severity among patients with AMI. However, our results are hypothesis-generating, and suggest that moderate SA may potentially offer cardioprotective benefits through enhanced coronary collaterals. These insights call for future research to explore the heterogeneity in ischemic preconditioning by SA severity and hypoxic burden to guide tailored clinical strategies for SA management in patients with AMI.

Keywords: sleep apnea, MI, myocardial infarction, cardiac MRI, Rentrop, ischemic preconditioning

Background

Obstructive sleep apnea (SA) occurs as a result of repetitive collapse of the upper airway during sleep, resulting in recurrent sympathetic arousals and intermittent hypoxemia (IH). Prevalence of SA is on the rise in part due to rising rates of obesity.[1] Recent estimates suggest that the global burden of moderate-to-severe SA exceeds 400 million individuals.[2] SA is associated with atherosclerosis and cardiovascular disease (CVD),[3] with a particularly high prevalence (between 60% to 70%) in patients hospitalized with an acute myocardial infarction (AMI).[4,5] Despite this, randomized trials have not demonstrated

Received: 9 August 2024
Accepted: 28 November 2024
Published: 9 January 2025

a cardiovascular benefit with continuous positive airway pressure (CPAP) – the mainstay of SA therapy – on composite cardiovascular outcomes.[6–9] Interestingly, recent evidence from a meta-analysis indicated a protective effect of CPAP therapy for stroke, but no significant effect on coronary outcomes.[10] Nevertheless, the mechanisms underlying this discrepancy in SA therapeutic effect on stroke versus myocardial infarction (MI) remain unclear. Our study therefore aims to address these knowledge gaps in SA and AMI, ultimately seeking to clarify how SA may influence surrogate cardiac metrics in patients with AMI. This will help enhance our understanding of a potential cardioprotective role of SA in a subset of patients by way of ischemic preconditioning.

Ischemic preconditioning in animal models has been demonstrated using a model of coronary occlusions followed by reperfusion, which may mimic the repetitive tissue hypoxia and reoxygenation experienced in SA.[11] Further, it is hypothesized that these mechanisms stimulate coronary collateral formation and cellular changes that combine to make cardiac myocytes less susceptible to acute ischemic injury.[12] The similarities between SA-induced IH and ischemic preconditioning from temporary interruptions in myocardial perfusion have led us to propose that SA could have a cardioprotective influence in AMI,[13–15] particularly through enhanced coronary collateral circulation.[16,17] Our prior work demonstrated that patients with AMI diagnosed with obstructive SA during hospitalization have less severe cardiac injury as measured by peak troponin-T levels 72 hours post-admission when compared to patients without SA.[13] This effect was independent of confounding variables, and the findings were confirmed in a subsequent study.[18] Additionally, in individuals with total coronary artery occlusion and AMI, SA was associated with enhanced coronary collateral circulation.[16,17] This supports the premise that SA, despite reported associations with CVD,[19–22] may potentially afford protection against myocardial injury in the context of AMI among a subgroup of patients.

To test this hypothesis, we conducted a study to assess if SA is associated with reduced infarct size and enhanced coronary collaterals during AMI. To our knowledge, no study has combined cardiac magnetic resonance imaging (CMR) to measure AMI size with coronary collateral assessment using angiography in AMI patients, both with and without SA. This integrated approach represents a novel direction in examining the interplay between the extent of myocardial injury and coronary collateral development. We hypothesized that patients with SA who have been exposed to recurrent IH before experiencing an AMI are likely to demonstrate more robust coronary collateral circulation and experience smaller myocardial infarct size.

Materials and Methods

We screened and recruited adults (age >21 years) admitted for AMI to two New York City hospitals – including Montefiore Medical Center (Bronx, NY), and Mount Sinai (New York, NY). Medically stable patients were approached for participation in the study after cardiac catheterization (Figure 1a). Informed written consent was obtained from all patients and the study was approved by the Montefiore Medical Center (IRB 10–03-061E) and Mount Sinai IRB (15–01256). Consented participants underwent Level III SA testing and CMR prior to discharge. Our inclusion criteria were: adult patients with a primary (first-ever) ST-Elevation MI (STEMI, defined by the 3rd Universal defintion[23]) or non-ST-elevation MI (NSTEMI) defined by standard criteria[23] who required percutaneous coronary intervention (PCI). We deferred enrollment of individuals with circulatory shock (defined as systolic blood pressure <90 mm Hg or requiring vasopressor treatment), those requiring mechanical ventilation, intra-aortic balloon pump, certain medications such as narcotics and sedatives, and those requiring supplemental oxygen. These patients were later reconsidered for recruitment once off the respective treatment and once hemodynamically stable. Exclusion criteria were inability to undergo CMR with contrast, such as those with an estimated glomerular filtration rate (eGFR) of less than 30mL/min/1.73 m^2, an intracardiac device, unwillingness or inability to provide informed consent, pregnancy, prior AMI or history of PCI or surgical revascularization (to minimize chronic multi-vessel disease with associated collateralization and remove the influence of in-stent thrombosis/restenosis or disease bypass grafts), known/treated SA, or no requirement for PCI.

Sleep Apnea Testing

Consented patients underwent portable SA testing using the Apnealink Plus monitor (ApneaLink™ device, ResMed Corporation, Poway, CA) during hospitalization, within 72 hours following PCI. Testing was administered by a trained respiratory or sleep technologist overnight. The Apnealink Plus monitor is a level III portable device, that provides accurate

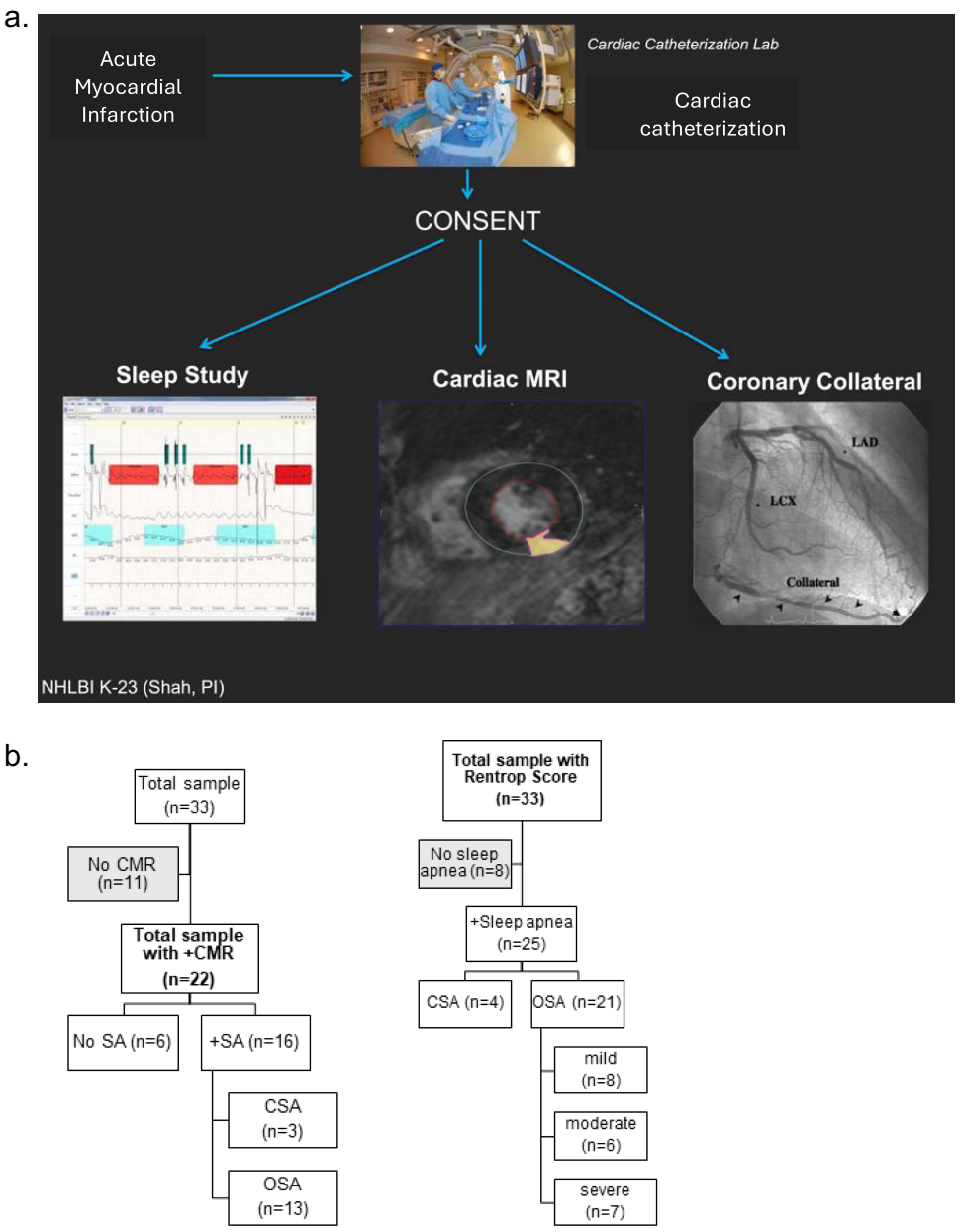

Figure 1 (**a**) Recruitment workflow. Patients with acute MI with cardiac catheterization were recruited. Recruited patients underwent a sleep study, cardiac MRI for assessment of left ventricular infarct size, and coronary collateral scoring using the Rentrop score. (**b**) Flow chart describing patient cohort. The right panel describes the entire sample with the angiographic Rentrop Score. The left panel highlights the subset of patients who underwent cardiac MRI for infarct size quantification.
Abbreviations: CSA, central sleep apnea; OSA, obstructive sleep apnea; SA, sleep apnea (all types).

identification of obstructive and central apneas via a chest belt for respiratory effort measures, apneas and hypopneas via nasal flow, snoring via a recording device, and blood oxygen saturation via pulse oximetry.[24] Sleep studies were scored in accordance with the American Academy of Sleep Medicine scoring rules for portable sleep studies.[25] An apnea was defined as at least 90% reduction in airflow lasting at least 10 seconds, and further distinguished as central or obstructive based on respiratory effort detected using respiratory inductance plethysmography (RIP). Hypopneas were defined as at least a 30% reduction in airflow for at least 10 seconds and associated with at least a 4% desaturation. The apnea-hypopnea index (AHI) was defined as the sum of all apneas plus hypopneas divided by total recording time. Central sleep apnea (CSA) was defined as >50% central events (apneas) per hour and a central AHI greater than or equal to 5. The patient and nurse were educated on the proper application of the monitor. Acquired sleep data included AHI, and oxygen desaturation index (ODI; the number of

https://doi.org/10.2147/NSS.S489788

times saturation dropped by 4% or more divided by total recording time). SA was categorized as: no sleep apnea (no-SA, AHI <5), mild SA (5≤AHI<15), moderate SA (15≤AHI<30), and severe SA (AHI ≥30).

CMR Protocol

Cardiac imaging was performed within 14 days following PCI. It was conducted at both hospitals using Philips Healthcare whole-body Achieva scanners with enhanced 80mT/m gradient systems. The 3T device features dedicated phased-array cardiac imaging coils and utilizes software release 2.6.3. The imaging protocol was standardized at both hospitals and imaging was performed before and after the intravenous administration of contrast – gadobutrol IV (a gadolinium-based contrast agent, 0.2 mmol/kg body weight).

Image Analysis

Image analysis was conducted using software (Medis) that provides automated contouring of acquired images. AMI size refers to the infarcted myocardium and is conventionally quantified by late gadolinium enhancement.[26] As such, after contrast administration, the contrast redistributes itself from the vascular compartment to the interstitial space, where a higher concentration of contrast is distributed in areas of MI than in normal myocardium.[26] The area of abnormal signal intensity was measured in the T2-weighted images and in the corresponding late-enhancement images by manual delineation (conducted by an experienced cardiothoracic radiologist who was blinded to clinical data).[27] A myocardial region was considered as affected if at least 10 adjacent myocardial pixels revealed a signal intensity of >5 standard deviations in late enhancement images.[28,29] The infarct size was calculated as infarct volume divided by the left ventricular (LV) myocardium volume.

Measurement of Coronary Collateral Score

Two independent trained cardiology fellows conducted the scoring of the collaterals using one of the most widely used angiographic grading system, the Rentrop Scoring system.[30] The cardiology fellows were blinded to clinical data. The scoring was defined as follows: Grade 0: no collaterals present; Grade 1: barely detectable coronary flow (contrast medium passes through collateral channels but fails to opacify the epicardial vessels at any time); Grade 2: partial collateral flow (contrast material enters but fails to opacify the target epicardial vessel completely); Grade 3: complete collateral flow/perfusion (contrast material enters and completely opacifies the target epicardial vessel). The Rentrop score ranges from 0 to 3, with higher scores indicating more developed coronary collaterals.

Outcomes and Covariate Measurement

The primary outcome was percent LV infarct size. Secondary outcomes included the Rentrop Score for coronary collateral scoring and blood biomarker assessments. Covariates were abstracted from the patient's Electronic Health Record (EHR) by trained research personnel. Medical information was confirmed by patient interviews when necessary (for missing data or confirmation). Obesity was defined as body mass index ≥ 30 kg/m^2 based on weight and height recorded in EHR. Hypertension was considered present with either a self-reported diagnosis by the patient, use of antihypertensive medication, or if medical records indicated an established diagnosis. Similarly, diabetes and dyslipidemia were considered present with either a self-reported diagnosis by the patient or if medical records indicated an established diagnosis, use of prescription drugs for diabetes, use of lipid lowering agents, or abnormal hemoglobin A1C (≥6.5%) on admission. Cigarette use was captured using a Tobacco Use Questionnaire (adapted from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL)),[31] which captures pack-years of tobacco use. Alcohol use was measured using Alcohol Use Questionnaire (also adapted from the HCHS/SOL).[31] Previous history of coronary heart disease was considered present with either a self-reported diagnosis of angina, "heart attack" or cardiac procedures, ie angioplasty, stent, coronary artery bypass graft surgery (CABG) or if indicated in EHR. Daytime sleepiness was measured using the Epworth Sleepiness Scale. Excessive daytime sleepiness was defined as a score >10 points.

Statistical Analysis

All analyses were performed using R statistical software. Baseline characteristics were summarized by SA category using descriptive statistics, and quantitative variables were compared using parametric or non-parametric statistical tests as appropriate. Group differences in infarct size and Rentrop Grade were compared using the non-parametric Wilcoxon rank-sum test or Fisher's exact test as appropriate, given the limitations in sample size. Interaction between SA (categorical) and statin use was also tested as an exploratory analysis, as our prior work has suggested that lipid-lowering agents such as statins may be important effect modifiers in the relationship between SA and CVD,[32] and a potentially key factor in predicting response to therapy.[33] Adjustments were made for multiple comparisons to control for the increased risk of type I errors. Analysis was conducted with a two-tailed alpha set to 0.05.

Results

We recruited 33 patients with AMI, who underwent PCI. The prevalence of SA was 76% (Figure 1b), categorized as no-SA, (n=8), mild SA (n=10), moderate SA (n=8), and severe SA (n=7). Of the 33 patients, 33% (n=11) did not undergo CMR due to an inability to obtain imaging during their inpatient hospitalization.

Baseline demographics and infarct size for those who underwent CMR are reported in Table 1 (n=22), of whom 16 had SA, and majority of whom presented with a STEMI (91%). There were no statistically significant differences in baseline demographics between the no-SA and SA groups. The majority of participants were male (mean $age_{no\text{-}SA}$=47.0 ±12.2, and mean age_{SA}=53.9±13.0) with an average BMI in the overweight range (mean $BMI_{no\text{-}SA}$=26.8±2.3, and mean BMI_{SA}=29.0±6.7). The mean AHI in the SA group was 21.7±16.4 events/hour, with a mean ODI of 18.2±15.5 desaturations per hour; Table 1. The AHI and ODI stratified by SA severity are presented in Table 2. There was no statistically significant difference in the median infarct size between the no-SA group versus the SA group (22% vs 28%, p=0.79, Wilcoxon rank-sum). We then stratified the data by SA severity (Table 2, Figure 2). While we did not find statistically significant differences, a U-shaped pattern emerged, where moderate SA patients had a smaller infarct size

Table 1 Baseline Demographics and Infarct Size of Patients Who Underwent Cardiac MRI (n=22)

	All Patients	No Sleep Apnea (AHI<5)	Sleep Apnea (AHI≥5)	p-Value
n	22	6	16	
Age (mean, SD)	52 (12.9)	47.0 (12.2)	53.9 (13.0)	0.28
Gender (male, %)	21 (95.5)	6 (100)	15 (93.8)	1.0
Ethnicity (Hispanic/Latino)	7 (31.8)	1 (16.6)	6 (37.5%)	0.62
Race				
White	12 (54.5)	4 (66.6)	8 (50%)	
Black	6 (27.3)	2 (33.3)	4 (25%)	
Asian	4 (18.2)	0 (0)	4 (25%)	
Body mass index (mean, SD)	28.4 (5.9)	26.8 (2.3)	29.0 (6.7)	0.45
Hypertension (yes, %)	10 (45.5)	3 (50.0)	7 (43.8)	1.0
Diabetes (yes, %)	5 (22.7)	2 (33.3)	3 (18.8)	0.88
Dyslipidemia (yes, %)	8 (36.4)	1 (16.7)	7 (43.8)	0.50
Stroke (no, %)[1]	22 (100)	6 (100)	16 (100)	
Ever smoked (yes, %)	14 (63.6)	5 (83.3)	9 (56.2)	0.50
Statins (yes, %)	5 (22.7)	1 (16.7)	4 (25.0)	1.0
Epworth Sleepiness Scale	7.1 (4.3)	5.2 (1.6)	7.8 (4.7)	0.065
AHI/ hour (mean, SD)	16.76 (16.1)	3.5 (0.6)	21.7 (16.4)	0.014
ODI/ hour (mean, SD)	14.1 (14.8)	3.2 (1.3)	18.2 (15.5)	0.03
STEMI (yes, %)	20 (91.0)	6 (100)	14 (87.5)	1.0
% infarcted (median, [IQR])	26 [12.5, 34.5]	22.0 [16.8, 31.8]	28.0 [15.5, 34.0]	0.79

Abbreviations: AHI, apnea-hypopnea index; IQR, Interquartile range; ODI, oxygen desaturation index; SD, Standard deviation; STEMI, ST Elevation Myocardial Infarction.

https://doi.org/10.2147/NSS.S489788

Table 2 Baseline Demographics of Patients Who Underwent Cardiac MRI Stratified by Sleep Apnea (SA) Severity

	No SA (AHI<5)	Mild SA (5≤AHI<15)	Moderate SA (15≤AHI<30)	Severe SA (AHI≥30)	p-Value
n	6	7	4	5	
Age (mean, SD)	47.0 (12.2)	51.7 (11.3)	50.3 (16.8)	59.8 (12.8)	0.45
Gender (male, %)	6 (100)	7 (100)	4 (100)	4 (100)	0.31
Body mass index (mean, SD)	26.8 (2.3)	31.9 (7.0)	26.3 (6.1)	27.2 (6.4)	0.32
Hypertension (yes, %)	3 (50.0)	3 (42.9)	1 (25.0)	3 (60.0)	0.76
Diabetes (yes, %)	2 (33.3)	1 (14.3)	0 (0.0)	2 (40.0)	0.44
Dyslipidemia (yes, %)	1 (16.7)	2 (28.6)	1 (25.0)	4 (80.0)	0.14
Ever smoked (yes, %)	5 (83.3)	3 (42.9)	2 (50.0)	4 (80.0)	0.36
Statins (yes, %)	1 (16.7)	2 (28.6)	0 (0.0)	2 (40.0)	0.52
AHI (mean, SD)	3.50 (0.55)	8.00 (2.58)	19.08 (3.34)	43.02 (9.16)	<0.001
ODI (mean, SD)	3.17 (1.33)	6.29 (2.81)	16.55 (6.05)	36.24 (14.19)	<0.001
% infarcted (median, [IQR])	22.0 [16.8, 31.8]	27.0 [23.8,32.5]	15.5 [9.0, 23.5]	34.0 [31.0, 53.0]	0.29

Abbreviations: AHI, apnea-hypopnea index; IQR, Interquartile range; ODI, oxygen desaturation index; SD, Standard deviation.

(median 15.5%, IQR 9.0–23.5) compared to all other groups (no SA [22.0%; IQR 16.8, 31.8], mild SA [27%; IQR 23.8, 32.5], and severe SA [34%; IQR 31, 53],p=0.12, Wilcoxon rank-sum). Further, statin use significantly modified the relationship between SA and infarct size such that patients with SA on statins (n=4, 25%) showed a significantly larger infarct size, compared to those with SA who were not on statins (n=12, 75%, p-value for interaction=0.02, Figure 3).

Coronary collateral circulation on angiograms was scored for the entire sample (n=33, of which 25 patients had SA) using the Rentrop scoring system, stratified by SA severity (Table 3). There were no patients with a Rentrop grade 3 score. Figure 4a shows the Rentrop score by SA status. Among those in the no-SA group, 75% showed no collaterals present (grade 0) with 25% of patients showing grade 2 collaterals (partial collateral flow). Overall, we did not find a statistically significant difference in Rentrop scores when stratified by SA status or severity. However, patients with SA (compared to those without SA) had a non-significant trend toward increased collateral circulation overall, with a greater proportion of patients having grade 1 (24%, barely detectable coronary flow) and grade 2 (40%) collaterals (Figure 4a,

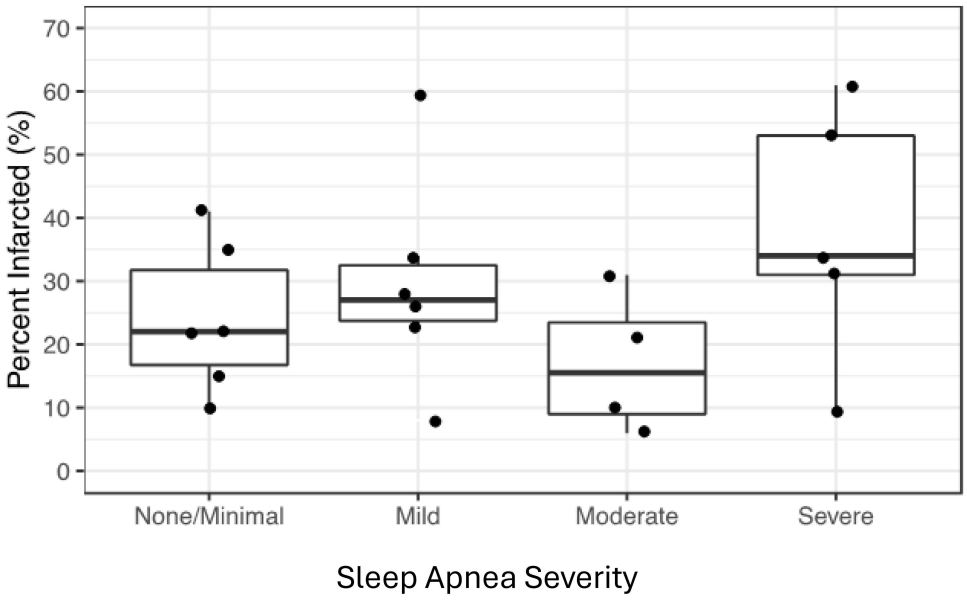

Figure 2 Infarct size by sleep apnea severity. Percent infarcted myocardium (y-axis), stratified by sleep apnea severity (x-axis). Patients with moderate sleep apnea have a trend toward a smaller infarct size compared to other groups.

https://doi.org/10.2147/NSS.S489788

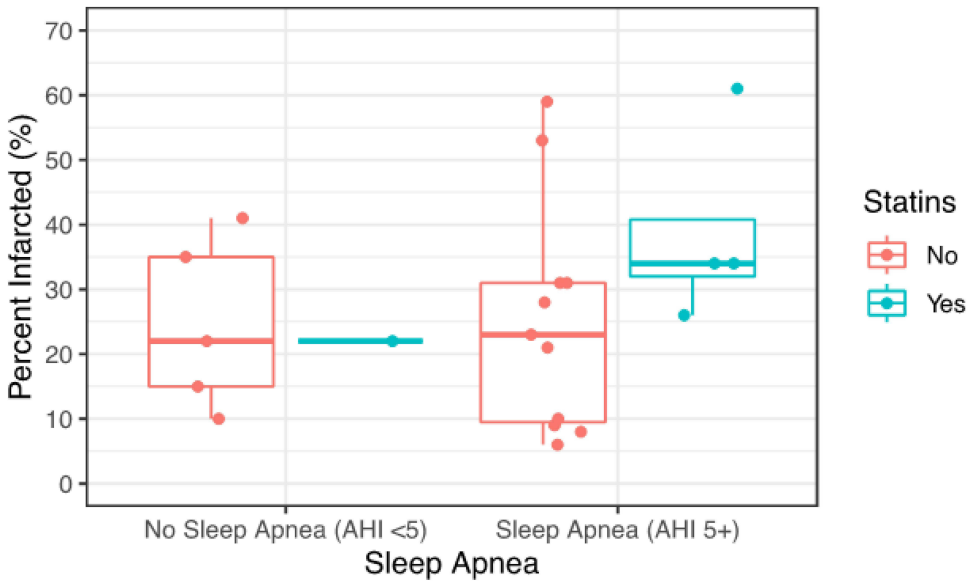

Figure 3 Sleep apnea and statin use interact to modulate infarct size. Percent infarcted myocardium (y-axis), stratified by sleep apnea severity and statin use (x-axis). Statin use was an effect modifier for the relationship between sleep apnea severity and percent infarcted, such that those who use statins and have sleep apnea have a larger percent-infarcted myocardium.
Abbreviation: AHI, apnea-hypopnea index.

p=0.12, Fisher's exact test). After stratification by SA severity (Figure 4b), we noted a trend toward a higher proportion of patients with moderate SA having Rentrop grade 2 collaterals compared to all other groups combined (moderate SA 62.5% versus other groups 28%, p = 0.08, Fisher's exact test).

Table 3 Rentrop Collateral Score Stratified by Sleep Apnea (SA) Severity (n=33)

	Total Sample	No SA (AHI<5)	Mild SA (5≤AHI<15)	Moderate SA (15≤AHI<30)	Severe SA (AHI≥30)	P-Value
n	33	8	10	8	7	
Age (mean, SD)	54.4 (11.5)	47.5 (10.9)	56.5 (9.8)	55.6 (15.3)	57.71 (7.8)	0.280
Gender (male, %)	29 (87.9)	7 (87.5)	8 (80.0)	7 (87.5)	7 (100.0)	0.671
Body mass index (mean, SD)	28.6 (5.9)	26.4 (6.1)	30.3 (5.6)	29.4 (6.1)	27.9 (6.4)	0.576
Coronary heart disease (yes, %)	20 (60.6)	6 (75.0)	6 (60.0)	4 (50.0)	4 (57.1)	0.775
Ever smoked (yes, %)	20 (60.6)	6 (75.0)	6 (60.0)	4 (50.0)	4 (57.1)	0.775
Hypertension (yes, %)	14 (42.4)	5 (62.5)	3 (30.0)	2 (25.0)	4 (57.1)	0.312
Dyslipidemia (yes, %)	11 (33.3)	2 (25.0)	3 (30.0)	3 (37.5)	3 (42.9)	0.885
Diabetes (yes, %)	5 (15.2)	3 (37.5)	0 (0.0)	1 (12.5)	1 (14.3)	0.176
AHI (median, IQR)	12 [5,24]	3.0 [2.8, 4.0]	7.5 [6.3,10.8]	19.5 [18.2, 21.0]	47.0 [35.0, 50.1]	<0.001
ODI (median, IQR)	8 [4,13]	3.5 [3.0, 4.0]	5.5 [4.0, 6.8]	14.5 [12.0, 21.8]	27.0 [10.0, 42.1]	<0.001
STEMI (yes, %)	29 [87.9]	7 (87.5)	10 (100)	6 (75)	6 (85.7)	
Multi-vessel Disease (yes, %)	22 [67.0]	5 (62.5)	6 (30.3)	5 (62.5)	6 (85.7)	0.71
Rentrop collateral grade (%)						0.222
0		6 (75.0)	4 (40.0)	1 (12.5)	4 (57.1)	
1		0 (0.0)	3 (30.0)	2 (25.0)	1 (14.3)	
2		2 (25.0)	3 (30.0)	5 (62.5)	2 (28.6)	

Abbreviations: AHI, apnea-hypopnea index; IQR, Interquartile range; ODI, oxygen desaturation index; SD, Standard deviation.

https://doi.org/10.2147/NSS.S489788

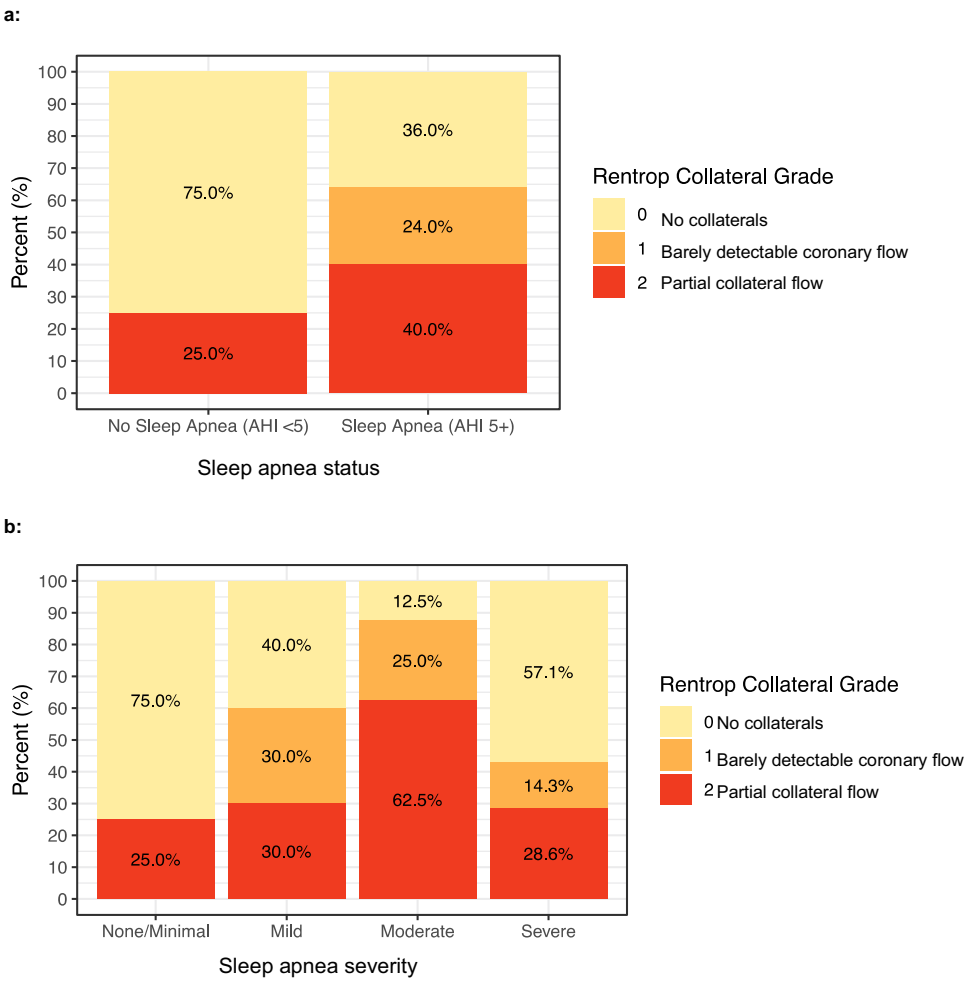

Figure 4 Rentrop collateral score by sleep apnea status. (**a**) Shows percent of patients (y-axis), stratified by sleep apnea status and the Rentrop grade (coronary collateral scoring system; x-axis). Compared to those without sleep apnea, a greater proportion of patients with sleep apnea had Rentrop grade 1 (barely detectable coronary flow) and grade 2 (partial collateral flow) coronary collaterals. (**b**) Further stratifies the Rentrop scoring by sleep apnea severity, showing that a higher proportion of patients with moderate sleep apnea had Rentrop grade 2 coronary collaterals.
Abbreviation: AHI, apnea-hypopnea index.

Discussion

To investigate the hypothesis that ischemic preconditioning in SA affords protection against myocardial injury, we performed cardiac imaging to evaluate whether SA is associated with reduced infarct size and increased coronary collateralization in patients with AMI. We did not find statistically significant differences in infarct size and Rentrop score by sleep apnea severity. However, our results suggest that patients with moderate SA had a trend toward smaller infarct size post-AMI and more enhanced coronary collaterals compared to those with no SA or with mild/severe SA. Moreover, we analyzed for effect modification of this relationship with statins, as our prior work has suggested that hypercholesterolemia and lipid-lowering therapies may be important factors in the relationship between SA and CVD.[32,33] We observed suggestive evidence for effect modification by statin use in this relationship, highlighting the potential value of incorporating statin use and hypercholesterolemia in future work to investigate the effect of SA on cardiovascular outcomes. Our results are hypothesis-generating and support recent literature highlighting the heterogeneity in sleep apnea with regard to CVD risk. Our findings extend our understanding of the IH and ischemic preconditioning phenomenon in SA, with suggestive evidence of increased coronary collateralization in AMI patients with moderate SA – potentially alluding that patients with moderate SA may demonstrate the most benefit from this phenomenon.

The theory of myocardial ischemic preconditioning[34] was demonstrated in seminal animal model experiments, where ischemic preconditioning was modeled via direct brief coronary artery occlusion and reperfusion, and a sustained occlusion resulted in a smaller infarct size.[11] Animal experiments have also utilized IH as a model of ischemic preconditioning (similar to animal models of SA), demonstrating similar reductions in infarct size.[35,36] Potential mechanisms for IH and SA-induced coronary collateralization include nitric oxide-regulated mobilization of endothelial progenitor cells (EPCs, known to mediate neovascularization through angiogenic growth factors) from the bone marrow to the injured myocardium,[37] and oxidative stress, which has shown to be increased in SA and is associated with increased collateralization.[38,39] For example, one study demonstrated that EPCs are higher in AMI patients with comorbid mild-to-moderate SA compared to those without, and also increased in healthy individuals after exposure to IH in vitro.[40] This suggests that mild-to-moderate SA may promote EPC-mediated compensatory angiogenesis, potentially improving endothelial function and providing cardioprotection in AMI.

Our main finding that patients with moderate SA show a trend toward smaller infarct sizes and increased coronary collateralization aligns with these aforementioned studies, though the results require confirmation in studies with larger sample sizes. Other human studies have also demonstrated that patients with SA (AHI>10, n=34) and coronary occlusion on angiography have augmented coronary collateral circulation (measured using the Rentrop score) compared to those without SA (AHI<10, n=19),[16] with a higher proportion of coronary collateral vessels (Rentrop≥1) among patients with an AMI and SA.[41] Another study demonstrated a significant and independent association between AHI and a Rentrop score >2 among patients with AMI.[17] On the other hand, human studies evaluating myocardial infarct size in all-comers with SA and AMI have demonstrated conflicting results with regard to infarct size and magnitude. For example, Buchner et al found that among patients with AMI, SA was in fact associated with a larger infarct size as measured by CMR.[42] However, in comparison to our study, the authors defined SA as a binary exposure (yes/no), combining the infarct size data for *all-comers* with SA. This may mask non-linear associations between SA severity and coronary collateralization/myocardial injury, therefore obscuring the heterogeneity of myocardial infarct size among SA patients as a result of an ischemic event. Contrary to the findings of Buchner et al, SA has been associated with increased proliferation and angiogenic capacity of EPCs during AMI,[40] and elevated plasma vascular endothelial growth factors (VEGF) levels which are suppressed by treatment of SA and IH with CPAP therapy.[43] Further, multiple studies have shown that higher AHI and SA are associated with lower peak troponin levels during AMI.[13,18]

Given these conflicting results, we conducted the first study to integrate both the Rentrop score for evaluation of coronary collateral circulation with cardiac imaging among patients with SA and AMI and evaluate the association of these outcomes with SA severity. In our cohort, a higher proportion of patients with moderate SA had Rentrop grade 2 collaterals and enhanced coronary collateral circulation compared to other SA-severity groups, despite the fact that moderate SA patients had a lower ODI compared to those with severe SA. Our findings contradict prior animal studies, where coronary collateral formation occurs in a dose-response manner only when exposed to severe hypoxemia,[44] as well as human studies suggesting that those with extensive coronary collaterals have a higher AHI and more severe SA.[17] By contrast, our results may suggest a more complex interplay between collateral formation and SA-induced IH, aligning with other animal studies demonstrating that cerebral collaterals can indeed occur at varying levels of hypoxemia, in a dose and duration dependent manner.[45] One possible explanation for our findings is that moderate SA may strike a balance of adaptive mechanisms, such as increased collaterals and enhanced endothelial function, which could counteract the adverse effects of hypoxia by way of increased collateral circulation. Additionally, IH may stimulate protective pathways that promote angiogenesis and improve cardiac outcomes. This interindividual heterogeneity in response to IH for collateral formation may be associated with the patient's ability to appropriately induce angiogenic factors such as VEGF.[46] These nuanced insights underscore the imperative for future studies to validate and further explore the intricacies of collateral formation in response to hypoxemia in SA, in association with angiogenic blood biomarkers. Future studies should also assess the influence of novel hypoxic burden metrics[47] on such outcomes.

Further, we analyzed for effect modification with statins, as our prior work has suggested that statins may be a key factor in modifying the relationship between SA and atherosclerosis[32] and potentially in predicting response to therapy.[33] We unexpectedly found that patients with SA on statins had a significantly larger infarct size compared to those with SA not on statins, potentially due to confounding by indication. Patients prescribed statins often have a higher burden of

coronary artery disease which may lead to more significant myocardial injury during AMI. Thus, the results we observed might reflect more advanced atherosclerotic disease in these patients rather than a direct effect of statin therapy. Our analysis did not adjust for various confounders that could influence outcomes. For instance, patients on statins may have additional cardiovascular risk factors such as diabetes or hypertension, or take antiplatelet agents and other medications that can complicate their clinical picture and affect myocardial perfusion and infarct size. Although this finding requires cautious interpretation, it may be important as it aligns with our prior work. We have previously found that hypercholesterolemia and the use of lipid-lowering agents may be critical factors influencing the complex relationship between SA and atherosclerosis.[32] Recent results from our post-hoc analysis of the ISAACC (Impact of Sleep Apnea Syndrome in the Evolution of Acute Coronary Syndrome) study[33] also demonstrated that hypercholesterolemia may be a key emerging factor in predicting response to CPAP in patients with SA and AMI.[48,49] Moreover, recent studies indicate that patients with SA, particularly those who are obese and exhibit metabolic abnormalities and increased visceral obesity,[50–54] face a significantly elevated risk of AMI and CVD. As such, our preliminary findings suggest the need for further research to elucidate the intricate interactions between statin use, comorbidities, and their collective impact on cardiovascular outcomes in patients with SA. Together, our data is hypothesis-generating, and suggests that repeated IH experienced by patients with moderate SA may potentially be cardioprotective in the context of AMI. This concept is supported by a recent study investigating common genetic variations and heterogeneity in individuals with and without SA, with certain elevated pathway-specific polygenic risk scores associated with protection for coronary artery disease in SA.[55] Moreover, in a large randomized controlled trial of patients with acute coronary syndrome, treatment of non-sleepy SA with CPAP in patients with AMI did not demonstrate a benefit on long-term CVD outcomes. As such, a subgroup of patients (possibly those with moderate SA) may theoretically dilute the effects of CPAP on CVD, potentially contributing to the null findings of this study.[33]

Our field is at a critical juncture, where decoding the heterogeneity of SA is crucial, particularly with regard to CVD risk prediction.[9] While CPAP is the cornerstone of SA therapy, multiple randomized controlled trials have failed to demonstrate a benefit of CPAP in the prevention of composite CVD events among non-sleepy patients with moderate-to-severe SA.[6–8,56] Therefore, recent studies have focused on identifying novel SA subgroups with increased cardiovascular risk to guide personalized therapeutic approaches.[57,58] Moreover, novel and promising therapies for SA are on the rise. A recent landmark trial investigating glucagon-like peptide-1 receptor agonists (GLP-1 RA) for the management of obesity-related SA, demonstrated significant improvements not only in SA severity, but also secondary outcomes including reductions in hypoxic burden, blood pressure, as well as biomarkers of inflammation such as C-reactive protein following weight loss in SA.[49] As such, we are now critically re-evaluating the need for *universal* SA treatment, exploring the heterogeneity in treatment response, and recognizing that CPAP may not be suitable for all.[59–61] Taken together with our results, as well as those of prior studies,[13,16–18,41] there is suggestive evidence that subgroups of patients with SA may be at least partially protected from CVD, and may not benefit from CPAP therapy. Although this requires rigorous confirmation, it may represent a major paradigm shift in the field of SA, as prior observational data has suggested a detrimental role of moderate-to-severe SA in all-comers on CVD risk. Future work may uncover that the duration of exposure and severity of SA, as well as comorbid disease status such as obesity may be an important effect modifier to account for in such analysis evaluating the impact of SA on ischemic preconditioning.

Limitations

Several methodological limitations should be considered in the interpretation of our study results. The study was initially powered to detect differences in the primary outcome by SA severity, with a plan to recruit a larger sample of patients. However, recruitment of patients with AMI to undergo CMR imaging posed unique challenges due to the acute nature of the patients' condition, and the logistical complexities of scheduling CMR within the hospital setting. Additionally, there was a marked reduction in the number of STEMI cases during the study period, which further impacted our ability to meet our sample size goals. To our knowledge, ours is the first study that combines CMR imaging and Rentrop scores to evaluate how SA influences cardiac imaging outcomes in AMI patients. As such, sample size limitations should be considered in light of the burden of recruitment for such a study, and the collaborative team science approach required for imaging and coronary collateral scoring. Given these limitations, we frame our results as hypothesis-generating rather

than conclusive. Ours was the first study to integrate both the Rentrop score for evaluation of coronary collateral circulation with cardiac imaging among patients with SA and AMI and evaluate the association of these outcomes with SA severity. Although our results did not reach statistical significance, recent literature highlights that simply relying on the merits of the p-value in causal inference may disregard important mechanistic or biological interpretations of effect sizes which may provide value.[62] The observed trends — particularly the potential for moderate SA to correlate with smaller infarct sizes and increased collateral circulation — highlight important avenues for further investigation. Future studies with larger sample sizes and multi-center collaborations to increase participant numbers are essential to (1) validate these findings and explore the underlying mechanisms involved, and (2) to investigate the heterogeneity of ischemic preconditioning by SA severity, or by other physiologic measures such as degree of hypoxic burden.[47] Further, although we recruited a diverse group of study-participants (approximately 50% non-white), we acknowledge that most studies investigating SA and CVD tend to be male-predominant, which is a limitation of our study as well - limiting our ability to generalize the findings to female participants. Future research in diverse settings and populations should validate our results along with longer term follow up on cardiac function, and explore how sex/gender, and demographic differences might differentially impact the relationship between SA and cardiovascular outcomes in patients with AMI. Additionally, future studies should also analyze the influence of additional confounding factors on these imaging outcomes in patients with SA, including obesity, diabetes, STEMI vs NSTEMI, culprit vessel lesion, single versus multi-vessel disease, etc., and confirm the finding of effect modifications with statins after adjusting for these variables.

Second, eleven patients who did not undergo CMR were excluded from the analysis of infarct size. While we recognize that this may introduce bias by systematically excluding a subset of participants, we considered this approach more rigorous than imputing missing data, especially given that percent myocardial infarction was our primary outcome. Imputation traditionally assumes data is missing at random, and with a third of our cohort missing CMR imaging data, we believed imputing the missing values could compromise the integrity of our results. Therefore, we employed a complete case approach, including only patients with complete data for the outcome variables of interest in the final analysis. This approach was chosen due to the limited sample size, in order to avoid incorrect assumptions or biased estimates that could lead to misleading conclusions. Third, we included patients with both, central (CSA) and obstructive SA, which may introduce variability and potentially bias the results toward the null, given that CSA has a distinct physiology compared to obstructive SA, and occurs most commonly in patients with heart failure. However, only a very small proportion of patients had CSA (4 in the Rentrop cohort, and 3 in the CMR cohort). Further, it is important to note that similar to obstructive SA, randomized trials evaluating PAP therapy in CSA have also not demonstrated a survival benefit.[63] In fact, a 2015 study showed an increase in cardiovascular mortality among patients with CSA on specialized PAP therapy (adaptive servo ventilation) despite improvements in nocturnal oxygen saturation,[64] though a more recent study reported conflicting findings with no effect on mortality.[65] This once again raises the question whether attenuating the consequences of sleep-disordered breathing such as IH may be detrimental in a subset of patients with the disease.[66] Additionally, we do not know whether these patients had SA prior to their AMI. Patients recruited for this study (following a cardiac event) may not be typical of SA patients presenting in sleep centers who are typically symptomatic.[67] However, it's well-established that the rate of SA in patients with coronary artery disease is notably high, with prior studies indicating rates above 60%.[68] Despite these patients often being asymptomatic, they are frequently referred for assessment at outpatient sleep centers, underscoring the relevance of these findings.

Despite these limitations, our results are impactful and important for the field. First, our main finding that patients with moderate SA have a trend toward a smaller infarct size and a higher proportion of coronary collateralization aligns with the premise of ischemic preconditioning in SA. These findings also align with prior human and animal studies supporting this concept,[11,13,16,35,36] reinforcing the reproducibility of our results. In parallel to our findings, others have demonstrated that SA is also associated with a smaller cerebral infarct volume/stroke severity in acute stroke, with less severe neurological injury[69] compared to those without SA. This suggests that a subset of SA patients may also have a neuroprotective effect in cerebrovascular disease. Second, the relationships and patterns we report here may support the hypothesis that IH during SA may result in ischemic preconditioning, potentially protecting a subset of SA patients from cardiac injury during AMI via mechanisms of coronary collateral formation. Importantly, our results do not refute data showing that obstructive SA is a risk factor for AMI,[19–22] rather they add nuance to the relationship between SA and

CVD – suggesting that some degree of IH in patients with moderate SA may provide cardiovascular benefit, while severe IH in patients with severe SA may not, given that those with severe SA in our cohort had the largest infarct size. If validated in larger studies, our results could inform clinical management by guiding the development of tailored treatment strategies for patients with AMI and SA. For instance, clinicians might consider integrating SA management into the overall care plan for AMI patients, with individualized risk assessments and decision-making regarding SA therapy based on SA severity, degree of hypoxic burden, and other demographic and clinical factors. Capturing this disease heterogeneity in SA outcomes can also inform future prognostic and predictive enrichment trials[70] to guide personalized therapeutic approaches based on subgroup-defining biology.

Conclusion

Among patients with AMI, we did not find a statistically significant difference in infarct size and Rentrop score by sleep apnea severity. However, trends captured in our results are hypothesis-generating, and suggest that moderate SA may potentially offer cardioprotective benefits in AMI through enhanced coronary collaterals and less severe myocardial injury, extending our understanding of IH and ischemic preconditioning in SA. These insights call for further mechanistic investigations and rigorous confirmation in future, larger studies to explore the heterogeneity in ischemic preconditioning by SA severity and hypoxic burden to guide tailored clinical strategies for SA management in patients with AMI.

Abbreviations

AHI, Apnea-Hypopnea Index; AMI, Acute Myocardial Infarction; BMI, Body Mass Index; CABG, Coronary Artery Bypass Graft; CMR, Cardiovascular/Cardia Magnetic Resonance; CPAP, Continuous Positive Airway Pressure; CSA, Central Sleep Apnea; CVD, Cardiovascular Disease; eGFR, Estimated Glomerular Filtration Rate; EHR, Electronic Health Record; EPC, Endothelial Progenitor Cells; HCHS/SOL, Hispanic Community Health Study/Study of Latinos; IQR, Interquartile Range; IH, Intermittent Hypoxemia; ISAACC, Impact of Sleep Apnea Syndrome in the Evolution of Acute Coronary Syndrome; LV, Left Ventricle; MI, Myocardial Infarction; NSTEMI, Non-ST-Elevation Myocardial Infarction; PCI, percutaneous coronary intervention; RIP, Respiratory Inductance Plethysmography; SA, Sleep Apnea; STEMI, ST-Elevation Myocardial Infarction; VEGF, Vascular Endothelial Growth Factor.

Data Sharing Statement

The data that support the findings of the study are available from the authors upon reasonable request. The data are not publicly available due to privacy or ethical restriction.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (name of institute/committee) and with the 1964 helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Montefiore Medical Center (IRB 10-03-061E) and Mount Sinai IRB (15-01256).

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Institution Where Work Was Performed

Division of Pulmonary, Critical Care, and Sleep Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA; Albert Einstein College of Medicine, Bronx, NY, USA

Acknowledgments

The abstract for this paper was presented at the American Thoracic Society Conference at a poster discussion session with interim findings. The poster's abstract was published in 'Poster Abstracts' in the ATS Journal: https://www.atsjournals.org/doi/abs/10.1164/ajrccmconference.2019.199.1_MeetingAbstracts.A4460?download=true

Author Contributions

All authors meet the following conditions:

1. Made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas.
2. Have drafted or written, or substantially revised or critically reviewed the article.
3. Have agreed on the journal to which the article will be submitted.
4. Reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage.
5. Agree to take responsibility and be accountable for the contents of the article.

Funding

The National Institute of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI) provided financial support in the form of a Research Career Development Award (5K23HL125923, PI: Neomi Shah). The sponsor had no role in the design or conduct of this research. Dr. Kundel has funding from the NIH/NHLBI K23HL161324 and AASM Foundation 274-BS-22. Dr. Cohen has funding from the Stony-Wold Herbert Grant. Dr. Redline reports partial funding from NIH/NHLBI R35HL1358181. Dr. Shah reports funding from the NIH/NHLBI R01HL143221 and R01HL168897.

Disclosure

Dr. Kundel reports fees from Zoll Respicardia. Dr. Cohen reports fees from Zoll Respicardia. Dr. Okamoto reports fees from Boston Scientific Japan and Abiomed Japan, unrelated to this topic. Dr. Kizer reports stock ownership in AbbVie, Abbott, Bristol Myers Squibb, Johnson & Johnson, Eli Lilly, Medtronic, Merck, and Pfizer. Dr Santos-Gallego reports grants from Robert A Winn Career Development Award, grants from Merck as a Principal Investigator of an Investigator-Initiated Study, advisory board for NovoNordisk, outside the submitted work. Dr. Redline has received consulting fees from Eli Lilly unrelated to this topic and is an unpaid member of the Scientific Advisory Board for ApniMed Inc; the National Sleep Foundation; and the Alliance of Sleep Apnea Partners. Dr. Shah reports fees from Zoll Respicardia. The authors report no other conflicts of interest in this work.

References

1. Ward ZJ, Bleich SN, Cradock AL. et al. Projected U.S. State-Level Prevalence of Adult Obesity and Severe Obesity. *N Engl J Med*. 2019;381(25):2440–2450. doi:10.1056/NEJMsa1909301
2. Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med*. 2019;7(8):687–698.
3. Javaheri S, Javaheri S, Somers VK, et al. Interactions of Obstructive Sleep Apnea With the Pathophysiology of Cardiovascular Disease, Part 1: JACC State-of-The-Art Review. *J Am Coll Cardiol*. 2024;84(13):1208–1223. doi:10.1016/j.jacc.2024.02.059
4. Lee CH, Khoo SM, Tai BC, et al. Obstructive sleep apnea in patients admitted for acute myocardial infarction. Prevalence, predictors, and effect on microvascular perfusion. *Chest*. 2009;135(6):1488–1495. doi:10.1378/chest.08-2336
5. Ludka O, Stepanova R, Vyskocilova M, et al. Sleep apnea prevalence in acute myocardial infarction--The Sleep Apnea in Post-acute Myocardial Infarction Patients (SAPAMI) Study. *Int J Cardiol*. 2014;176(1):13–19. doi:10.1016/j.ijcard.2014.06.020
6. McEvoy RD, Antic NA, Heeley E, et al. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. *N Engl J Med*. 2016;375(10):919–931. doi:10.1056/NEJMoa1606599
7. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunstrom E. Effect of Positive Airway Pressure on Cardiovascular Outcomes in Coronary Artery Disease Patients with Nonsleepy Obstructive Sleep Apnea. The RICCADSA Randomized Controlled Trial. *Am J Respir Crit Care Med*. 2016;194(5):613–620. doi:10.1164/rccm.201601-0088OC
8. Sanchez-de-la-Torre M, Sanchez-de-la-Torre A, Bertran S, et al. Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial. *Lancet Respir Med*. 2020;8(4):359–367. doi:10.1016/S2213-2600(19)30271-1
9. Cohen O, Kundel V, Barbé F, et al. The Great Controversy of Obstructive Sleep Apnea Treatment for Cardiovascular Risk Benefit: advancing the Science Through Expert Consensus. *Ann Am Thorac Soc*. 2024;2024:1.
10. Javaheri S, Javaheri S, Gozal D, et al. Treatment of OSA and its Impact on Cardiovascular Disease, Part 2: JACC State-of-The-Art Review. *J Am Coll Cardiol*. 2024;84(13):1224–1240. doi:10.1016/j.jacc.2024.07.024
11. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation*. 1986;74(5):1124–1136. doi:10.1161/01.CIR.74.5.1124

12. Buja LM. Pathobiology of Myocardial Ischemia and Reperfusion Injury: models, Modes, Molecular Mechanisms, Modulation, and Clinical Applications. *Cardiol Rev*. 2023;31(5):252–264. doi:10.1097/CRD.0000000000000440
13. Shah N, Redline S, Yaggi HK, et al. Obstructive sleep apnea and acute myocardial infarction severity: ischemic preconditioning? *Sleep Breath*. 2013;17(2):819–826. doi:10.1007/s11325-012-0770-7
14. Lavie P, Lavie L. Unexpected survival advantage in elderly people with moderate sleep apnoea. *J Sleep Res*. 2009;18(4):397–403. doi:10.1111/j.1365-2869.2009.00754.x
15. Lavie P, Lavie L, Herer P. All-cause mortality in males with sleep apnoea syndrome: declining mortality rates with age. *Eur Respir J*. 2005;25(3):514–520. doi:10.1183/09031936.05.00051504
16. Steiner S, Schueller PO, Schulze V, Strauer BE. Occurrence of coronary collateral vessels in patients with sleep apnea and total coronary occlusion. *Chest*. 2010;137(3):516–520. doi:10.1378/chest.09-1136
17. Summerer V, Arzt M, Fox H, et al. Occurrence of Coronary Collaterals in Acute Myocardial Infarction and Sleep Apnea. *J Am Heart Assoc*. 2021;10(15):e020340. doi:10.1161/JAHA.120.020340
18. Sánchez-de-la-Torre A, Soler X, Barbé F, et al. Cardiac Troponin Values in Patients With Acute Coronary Syndrome and Sleep Apnea: a Pilot Study. *Chest*. 2018;153(2):329–338. doi:10.1016/j.chest.2017.06.046
19. Peker Y, Carlson J, Hedner J. Increased incidence of coronary artery disease in sleep apnoea: a long-term follow-up. *Eur Respir J*. 2006;28(3):596–602. doi:10.1183/09031936.06.00107805
20. Shah NA, Yaggi HK, Concato J, Mohsenin V. Obstructive sleep apnea as a risk factor for coronary events or cardiovascular death. *Sleep Breath*. 2010;14(2):131–136. doi:10.1007/s11325-009-0298-7
21. Martinez D, Klein C, Rahmeier L, et al. Sleep apnea is a stronger predictor for coronary heart disease than traditional risk factors. *Sleep Breath*. 2012;16(3):695–701. doi:10.1007/s11325-011-0559-0
22. Martinez D, da Silva RP, Klein C, et al. High risk for sleep apnea in the Berlin questionnaire and coronary artery disease. *Sleep Breath*. 2012;16(1):89–94. doi:10.1007/s11325-010-0460-2
23. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *J Am Coll Cardiol*. 2007;50(22):2173–2195. doi:10.1016/j.jacc.2007.09.011
24. Erman MK, Stewart D, Einhorn D, Gordon N, Casal E. Validation of the ApneaLink for the screening of sleep apnea: a novel and simple single-channel recording device. *J Clin Sleep Med*. 2007;3(4):387–392. doi:10.5664/jcsm.26861
25. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med*. 2012;8(5):597–619. doi:10.5664/jcsm.2172
26. Bulluck H, Dharmakumar R, Arai AE, Berry C, Hausenloy DJ. Cardiovascular Magnetic Resonance in Acute ST-Segment-Elevation Myocardial Infarction: recent Advances, Controversies, and Future Directions. *Circulation*. 2018;137(18):1949–1964. doi:10.1161/CIRCULATIONAHA.117.030693
27. Abdel-Aty H, Zagrosek A, Schulz-Menger J, et al. Delayed enhancement and T2-weighted cardiovascular magnetic resonance imaging differentiate acute from chronic myocardial infarction. *Circulation*. 2004;109(20):2411–2416. doi:10.1161/01.CIR.0000127428.10985.C6
28. Bondarenko O, Beek AM, Hofman MB, et al. Standardizing the definition of hyperenhancement in the quantitative assessment of infarct size and myocardial viability using delayed contrast-enhanced CMR. *J Cardiovasc Magn Reson*. 2005;7(2):481–485. doi:10.1081/JCMR-200053623
29. Eitel I, Desch S, Fuernau G, et al. Prognostic significance and determinants of myocardial salvage assessed by cardiovascular magnetic resonance in acute reperfused myocardial infarction. *J Am Coll Cardiol*. 2010;55(22):2470–2479. doi:10.1016/j.jacc.2010.01.049
30. Cohen M, Rentrop KP. Limitation of myocardial ischemia by collateral circulation during sudden controlled coronary artery occlusion in human subjects: a prospective study. *Circulation*. 1986;74(3):469–476. doi:10.1161/01.CIR.74.3.469
31. Klugman M, Hosgood III HD, Hua S, et al. A longitudinal analysis of nondaily smokers: the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Ann Epidemiol*. 2020;49:61–67. doi:10.1016/j.annepidem.2020.06.007
32. Newman SB, Kundel V, Matsuzaki M, et al. Sleep apnea, coronary artery calcium density and cardiovascular events: results from the Multi-Ethnic Study of Atherosclerosis (Mesa). *J Clin Sleep Med*. 2021;17(10):2075–2083. doi:10.5664/jcsm.9356
33. Sánchez-de-la-Torre M, Sánchez-de-la-Torre A, Bertran S, et al. Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial. *Lancet Respir Med*. 2020;8(4):359–367.
34. Mallet RT, Manukhina EB, Ruelas SS, Caffrey JL, Downey HF. Cardioprotection by intermittent hypoxia conditioning: evidence, mechanisms, and therapeutic potential. *Am J Physiol Heart Circ Physiol*. 2018;315(2):H216–H232. doi:10.1152/ajpheart.00060.2018
35. Zong P, Setty S, Sun W, et al. Intermittent hypoxic training protects canine myocardium from infarction. *Exp Biol Med*. 2004;229(8):806–812. doi:10.1177/153537020422900813
36. Xu WQ, Yu Z, Xie Y, et al. Therapeutic effect of intermittent hypobaric hypoxia on myocardial infarction in rats. *Basic Res Cardiol*. 2011;106(3):329–342. doi:10.1007/s00395-011-0159-y
37. Jelic S, Padeletti M, Kawut SM, et al. Inflammation, oxidative stress, and repair capacity of the vascular endothelium in obstructive sleep apnea. *Circulation*. 2008;117(17):2270–2278. doi:10.1161/CIRCULATIONAHA.107.741512
38. Schulz R, Mahmoudi S, Hattar K, et al. Enhanced release of superoxide from polymorphonuclear neutrophils in obstructive sleep apnea. Impact of continuous positive airway pressure therapy. *Am J Respir Crit Care Med*. 2000;162(2):566–570. doi:10.1164/ajrccm.162.2.9908091
39. Demirbag R, Gur M, Yilmaz R, Kunt AS, Erel O, Andac MH. Influence of oxidative stress on the development of collateral circulation in total coronary occlusions. *Int J Cardiol*. 2007;116(1):14–19. doi:10.1016/j.ijcard.2006.02.012
40. Berger S, Aronson D, Lavie P, Lavie L. Endothelial progenitor cells in acute myocardial infarction and sleep-disordered breathing. *Am J Respir Crit Care Med*. 2013;187(1):90–98. doi:10.1164/rccm.201206-1144OC
41. Ben Ahmed H, Boussaid H, Longo S, et al. Impact of obstructive sleep apnea in recruitment of coronary collaterality during inaugural acute myocardial infarction. *Ann Cardiol Angeiol*. 2015;64(4):273–278. doi:10.1016/j.ancard.2015.01.014
42. Buchner S, Satzl A, Debl K, et al. Impact of sleep-disordered breathing on myocardial salvage and infarct size in patients with acute myocardial infarction. *Eur Heart J*. 2014;35(3):192–199. doi:10.1093/eurheartj/eht450
43. Lavie L, Kraiczi H, Hefetz A, et al. Plasma vascular endothelial growth factor in sleep apnea syndrome: effects of nasal continuous positive air pressure treatment. *Am J Respir Crit Care Med*. 2002;165(12):1624–1628. doi:10.1164/rccm.20110-040OC

44. Aghajanian A, Zhang H, Buckley BK, Wittchen ES, Ma WY, Faber JE. Decreased inspired oxygen stimulates de novo formation of coronary collaterals in adult heart. *J Mol Cell Cardiol*. 2021;150:1–11. doi:10.1016/j.yjmcc.2020.09.015
45. Zhang H, Rzechorzek W, Aghajanian A, Faber JE. Hypoxia induces de novo formation of cerebral collaterals and lessens the severity of ischemic stroke. *J Cereb Blood Flow Metab*. 2020;40(9):1806–1822. doi:10.1177/0271678X20924107
46. Schultz A, Lavie L, Hochberg I, et al. Interindividual heterogeneity in the hypoxic regulation of VEGF: significance for the development of the coronary artery collateral circulation. *Circulation*. 1999;100(5):547–552. doi:10.1161/01.CIR.100.5.547
47. Azarbarzin A, Sands SA, Stone KL, et al. The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study. *Eur Heart J*. 2019;40(14):1149–1157. doi:10.1093/eurheartj/ehy624
48. Cohen O, Sanchez-de-la-Torre M, Al-Taie Z, et al. Heterogeneous Effects of Continuous Positive Airway Pressure in Non-Sleepy Obstructive Sleep Apnea on Cardiovascular Disease Outcomes: post Hoc Machine Learning Analysis of the ISAACC Trial (ECSACT Study). *Ann Am Thorac Soc*. 2024;21(7):1074–1084. doi:10.1513/AnnalsATS.202309-799OC
49. Malhotra A, Grunstein RR, Fietze I, et al. Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity. *N Engl J Med*. 2024;391 (13):1193–1205. doi:10.1056/NEJMoa2404881
50. Kundel V, Lehane D, Ramachandran S, et al. Measuring Visceral Adipose Tissue Metabolic Activity in Sleep Apnea Utilizing Hybrid (18)F-FDG PET/MRI: a Pilot Study. *Nat Sci Sleep*. 2021;13:1943–1953. doi:10.2147/NSS.S327341
51. Hu J, Cai X, Li N, et al. Association Between Triglyceride Glucose Index-Waist Circumference and Risk of First Myocardial Infarction in Chinese Hypertensive Patients with Obstructive Sleep Apnoea: an Observational Cohort Study. *Nat Sci Sleep*. 2022;14:969–980. doi:10.2147/NSS.S362101
52. Cai X, Song S, Hu J, et al. Body roundness index improves the predictive value of cardiovascular disease risk in hypertensive patients with obstructive sleep apnea: a cohort study. *Clin Exp Hypertens*. 2023;45(1):2259132. doi:10.1080/10641963.2023.2259132
53. Zhao J, Cai X, Hu J, et al. J-Shaped Relationship Between Weight-Adjusted-Waist Index and Cardiovascular Disease Risk in Hypertensive Patients with Obstructive Sleep Apnea: a Cohort Study. *Diabetes Metab Syndr Obes*. 2024;17:2671–2681. doi:10.2147/DMSO.S469376
54. Cai X, Li N, Hu J, et al. Nonlinear Relationship Between Chinese Visceral Adiposity Index and New-Onset Myocardial Infarction in Patients with Hypertension and Obstructive Sleep Apnoea: insights from a Cohort Study. *J Inflamm Res*. 2022;15:687–700. doi:10.2147/JIR.S351238
55. Goodman MO, Cade BE, Shah NA, et al. Pathway-Specific Polygenic Risk Scores Identify Obstructive Sleep Apnea-Related Pathways Differentially Moderating Genetic Susceptibility to Coronary Artery Disease. *Circ Genom Precis Med*. 2022;15(5):e003535. doi:10.1161/ CIRCGEN.121.003535
56. Barbe F, Duran-Cantolla J, Sanchez-de-la-Torre M, et al. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. *JAMA*. 2012;307(20):2161–2168. doi:10.1001/jama.2012.4366
57. Zapater A, Sánchez-de-la-Torre M, Benítez ID, et al. The Effect of Sleep Apnea on Cardiovascular Events in Different Acute Coronary Syndrome Phenotypes. *Am J Respir Crit Care Med*. 2020;202(12):1698–1706. doi:10.1164/rccm.202004-1127OC
58. Mazzotti DR, Keenan BT, Lim DC, Gottlieb DJ, Kim J, Pack AI. Symptom Subtypes of Obstructive Sleep Apnea Predict Incidence of Cardiovascular Outcomes. *Am J Respir Crit Care Med*. 2019;200(4):493–506. doi:10.1164/rccm.201808-1509OC
59. Kundel V, Cohen O, Shah N. Reimagining obstructive sleep apnoea: a new era for sleep medicine. *Lancet Respir Med*. 2023;11(11):956–958. doi:10.1016/S2213-2600(23)00372-7
60. Gottlieb DJ, Lederer DJ, Kim JS, et al. Effect of positive airway pressure therapy of obstructive sleep apnea on circulating Angiopoietin-2. *Sleep Med*. 2022;96:119–121. doi:10.1016/j.sleep.2022.05.007
61. Kundel V, Cohen O, Khan S, et al. Advanced Proteomics and Cluster Analysis for Identifying Novel Obstructive Sleep Apnea Subtypes before and after Continuous Positive Airway Pressure Therapy. *Ann Am Thorac Soc*. 2023;20(7):1038–1047. doi:10.1513/AnnalsATS.202210-897OC
62. Lederer DJ, Bell SC, Branson RD, et al. Control of Confounding and Reporting of Results in Causal Inference Studies. Guidance for Authors from Editors of Respiratory, Sleep, and Critical Care Journals. *Ann Am Thorac Soc*. 2019;16(1):22–28. doi:10.1513/AnnalsATS.201808-564PS
63. Bradley TD, Logan AG, Kimoff RJ, et al. Continuous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med*. 2005;353 (19):2025–2033. doi:10.1056/NEJMoa051001
64. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure. *N Engl J Med*. 2015;373(12):1095–1105. doi:10.1056/NEJMoa1506459
65. Bradley TD, Logan AG, Lorenzi Filho G, et al. Adaptive servo-ventilation for sleep-disordered breathing in patients with heart failure with reduced ejection fraction (ADVENT-HF): a multicentre, multinational, parallel-group, open-label, Phase 3 randomised controlled trial. *Lancet Respir Med*. 2024;12(2):153–166. doi:10.1016/S2213-2600(23)00374-0
66. Naughton MT. Cheyne-Stokes respiration: friend or foe? *Thorax*. 2012;67(4):357–360. doi:10.1136/thoraxjnl-2011-200927
67. Reynor A, McArdle N, Shenoy B, et al. Continuous positive airway pressure and adverse cardiovascular events in obstructive sleep apnea: are participants of randomized trials representative of sleep clinic patients? *Sleep*. 2022;45(4). doi:10.1093/sleep/zsab264.
68. Glantz H, Thunström E, Herlitz J, et al. Occurrence and predictors of obstructive sleep apnea in a revascularized coronary artery disease cohort. *Ann Am Thorac Soc*. 2013;10(4):350–356. doi:10.1513/AnnalsATS.201211-106OC
69. Festic N, Alejos D, Bansal V, et al. Sleep Apnea in Patients Hospitalized With Acute Ischemic Stroke: underrecognition and Associated Clinical Outcomes. *J Clin Sleep Med*. 2018;14(1):75–80. doi:10.5664/jcsm.6884
70. Stanski NL, Wong HR. Prognostic and predictive enrichment in sepsis. *Nat Rev Nephrol*. 2020;16(1):20–31. doi:10.1038/s41581-019-0199-3