Journal of Cardiovascular Nursing
Vol. 00, No. 0, pp. 00–00

Ischemic Preconditioning Is Present in Patients With Non–ST Elevation Myocardial Infarction Screened With Electrocardiogram-Derived Moderate Obstructive Sleep Apnea

Elizabeth Borczynski, MS, RN, CNS; Sukardi Suba, PhD, RN; Lynda A. Mackin, PhD, RN, AGPCNP-BC, CCNS; David W. Mortara, PhD; Fabio Badilini, PhD; George W. Rodway, PhD, RN, APRN; Michele M. Pelter, PhD, RN, FAHA

Background: Obstructive sleep apnea (OSA) is associated with an increased risk of cardiovascular events, including acute coronary syndrome (ACS). There is conflicting evidence that suggests OSA has a cardioprotective effect (ie, lower troponin), via ischemic preconditioning, in patients with ACS. **Purpose:** This study had 2 aims: (1) compare peak troponin between non–ST elevation (NSTE) ACS patients with and without moderate OSA identified using a Holter-derived respiratory disturbance index (HDRDI) and (2) determine the frequency of transient myocardial ischemia (TMI) between NSTE-ACS patients with and without moderate HDRDI. **Method:** This was a secondary analysis. Obstructive sleep apnea events were identified from 12-lead electrocardiogram Holter recordings using QRSs, R-R intervals, and the myogram. Moderate OSA was defined as an HDRDI of greater than or equal to 15 events per hour. Transient myocardial ischemia was defined as greater than or equal to 1 mm of ST-segment ↑ or ↓, in 1 or more electrocardiogram lead, lasting at least 1 minute. **Results:** In 110 patients with NSTE-ACS, 39% (n = 43) had moderate HDRDI. Peak troponin was lower in patients with moderate HDRDI (6.8 ng/mL yes vs 10.2 ng/mL no; $P = .037$). There was a trend for fewer TMI events, but there were no differences (16% yes vs 30% no; $P = .081$). **Conclusions:** Non–ST elevation ACS patients with moderate HDRDI have less cardiac injury than those without moderate HDRDI measured using a novel electrocardiogram-derived method. These findings corroborate previous studies suggesting a possible cardioprotective effect of OSA in patients with ACS via ischemic precondition. There was a trend for fewer TMI events in patients with moderate HDRDI, but there was no statistical difference. Future research should explore the underlying physiologic mechanisms of this finding.

KEY WORDS: acute coronary syndrome, electrocardiographic derived respirations, electrocardiography monitoring, ischemic preconditioning, obstructive sleep apnea

Elizabeth Borczynski, MS, RN, CNS
Nurse Professional Development Specialist - Interventional Platform Education, Stanford Health Care, Palo Alto, California. At the time of the study, Elizabeth Borczynski was a Graduate Student at the University of California San Francisco, School of Nursing.

Sukardi Suba, PhD, RN
Postdoctoral Associate, School of Nursing, University of Rochester, New York.

Lynda A. Mackin, PhD, RN, AGPCNP-BC, CCNS
Clinical Professor, Department of Physiological Nursing, University of California San Francisco School of Nursing.

David W. Mortara, PhD
Professor and Founder, Center for Physiologic Research, Department of Physiologic Research, University of California San Francisco School of Nursing.

Fabio Badilini, PhD
Professor, Director, Center for Physiologic Research, Department of Physiological Nursing, University of California San Francisco School of Nursing.

George W. Rodway, PhD, RN, APRN
Adjunct Professor of Family Medicine – Sports Medicine, School of Medicine, University of Nevada, Reno.

Michele M. Pelter, PhD, RN, FAHA
Associate Professor and Director, ECG Monitoring Research Lab, and Associate Translational Scientist, Center for Physiologic Research, Department of Physiological Nursing, University of California San Francisco School of Nursing.

This study was supported by grant R21NR011202 (PI: M.M.P.) provided by the National Institutes of Health (NIH) and by the National Center for Advancing Translational Sciences, NIH, through UCSF-CTSI grant number UL1 TR001872-06. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

The authors have no conflicts of interest to disclose.

Correspondence
Sukardi Suba, PhD, RN, 601 Elmwood Ave, Box SON 2W319, Rochester, NY 14642 (sukardi_suba@urmc.rochester.edu).

DOI: 10.1097/JCN.0000000000000926

Evidence shows that obstructive sleep apnea (OSA) is associated with an increased risk of major adverse cardiovascular events, including acute coronary syndrome (ACS).[1] The prevalence of OSA in patients with ACS is as high as 60%.[2] Physiologic responses to OSA that may exacerbate ACS include hypoxia, arousal due to sympathetic activation, oxidative stress, and hypercoagulability.[3–5] Given these mechanisms, it has been hypothesized that ACS patients with OSA may have more severe myocardial damage (ie, higher troponin) and/or ongoing myocardial ischemia.

However, there is conflicting evidence about whether more severe myocardial ischemia is present in patients with OSA due to intermittent hypoxemia (apnea) associated with this pathology. In a hospital-based study that used respiratory polygraph to assess OSA, although no association between OSA and cardiac events was found, hospitalization was longer in those with OSA.[6] The investigators found that peak plasma troponin levels were higher in patients with OSA compared with those without OSA, which might indicate that the infarct size was larger in those with OSA and might explain the longer length of hospitalization. This latter finding is opposite to a study by Shah and coworkers[7] who found that ACS patients with mild OSA (<5 events/h) measured by polygraph had lower troponin levels than those without OSA after adjustments for age, race, current smoker, other cardiovascular risk factors, and/or comorbidities. The investigators suggested that OSA, present before the acute ACS event, may have a cardioprotective effect from "ischemic precondition," a finding supported in animal studies.[8–10] Similar to Shah et al's study, Sánchez-De-La-Torre and coworkers[11] found that cardiac troponin levels were lower in ACS patients with severe OSA (>32 events/h) as compared with those without OSA. Ischemic preconditioning is defined as intermittent short periods of ischemia that make the myocardium become more resistant to subsequent ischemic insult.[12]

Two studies in which authors examined in-hospital clinical outcomes in ACS patients with and without OSA found that OSA was linked to recurrent angina (ie, ongoing myocardial ischemia)[13,14] and death.[13] However, authors of both studies used a self-report questionnaire to screen for OSA, and recurrent angina was measured by patient-reported symptoms. Using only symptoms to identify recurrent ischemia is problematic given research showing that these events are often asymptomatic (ie, silent) when measured using the noninvasive criterion-standard 12-lead electrocardiogram (ECG).[15,16] Therefore, these studies likely underreported recurrent angina. Given the evidence suggesting that myocardial preconditioning is present in ACS patients with OSA using troponin blood levels, we hypothesized that transient myocardial ischemia would also be lower. However, to date, recurrent ischemia in OSA has not been examined using continuous 12-lead ECG Holter recordings. Findings from such a study could corroborate whether preconditioning exists and enhance our understanding of the underlying physiologic mechanisms of ischemia in ACS patients with OSA.

Although the gold-standard test used to diagnose OSA is polysomnography, this test is not practical in hospitalized patients with ACS. Previous studies have examined ECG-derived methods to identify abnormal respirations associated with OSA and Cheyne-Stokes respirations.[17–22] This method is intriguing given that hospitalized patients with ACS have continuous ECG monitoring as a standard of care. In this study, we take the novel approach of screening for moderate/severe OSA (≥15 events/h) using a Holter-derived respiratory disturbance index (HDRDI). The continuous 12-lead ECG data also allowed our team the opportunity to identify transient myocardial ischemia objectively. Therefore, the purpose of this study was 2-fold: (1) examine the severity of myocardial injury using peak cardiac troponin levels between non–ST elevation (NSTE) ACS patients with and without moderate HDRDI and (2) determine the frequency of transient myocardial ischemia between NSTE-ACS patients with and without moderate HDRDI.

Methods

Study Design

This was a secondary analysis using data from the COMPARE Study, the methods of which have been previously published.[16,23] Briefly, the COMPARE Study was a prospective observational study conducted at 3 private hospitals in California and Nevada. The primary study was designed to evaluate the frequency of transient myocardial ischemia in patients presenting to the hospital with suspected ACS treated with either an early invasive strategy (ie, cardiac catheterization < 24 hours after admission, before stress testing or determining whether pharmacological management fails) or initial conservative strategy (ie, cardiac catheterization only if aggressive medical treatment fails measured by recurrent symptoms, new ECG changes, or a positive stress test). The study was approved by each hospital's institutional review board, and informed written consent was obtained from each patient at enrollment. English-speaking patients who presented to the emergency department, or within 8 hours after hospital admission, for symptoms suggestive of ACS (ie, chest pain, shortness of breath, arm pain, diaphoresis, or symptoms at rest) were invited to participate in the primary study. Patients were excluded if they were admitted for ST-segment elevation myocardial infarction, were comatose or obtunded, had a major psychiatric disorder, or were in isolation precautions. Also excluded were patients with left bundle branch block or ventricular paced rhythms because these known ECG confounders make it difficult to determine whether true myocardial ischemia is present.[23]

Sample

For this study, only those patients enrolled in the COMPARE Study who were ultimately given a diagnosis of NSTE-ASC were included. The diagnosis of NSTE-ACS was defined using the standard definition of cardiac biomarker evidence of myocardial necrosis (eg, positive CK-MB or troponin) without new ST-segment elevation.[24] At the time of the primary study, a troponin of greater than 0.04 ng/mL was considered a positive test for NSTE-ACS. Although the COMPARE Study enrolled a total of 488 patients, 110 (23%) were ultimately given a diagnosis of NSTE-ACS and are thus included in this secondary analysis.

12-Lead Holter Data Acquisition

All patients included in the primary study had Holter ECG recordings. A 12-lead ECG Holter recorder (H12+ Digital Holter Recorder Mortara Instruments, Milwaukee, Wisconsin) was applied as soon as possible after presentation to the emergency department or within 8 hours of admission for patients admitted during the time our research team was not present in the hospital. Before initiating the Holter recording, a unique study identification number assigned at enrollment was typed into the Holter recorder. The 12-lead Holter recorders were "black boxes"; hence, the data were not available to clinicians for decision making, and there were no alarms generated. In addition, the ECG data were analyzed after hospital discharge.

Before applying the Holter recorder to the patient's torso, a research nurse carefully prepped the patient's torso to remove any dirt, oils, or creams that may interfere with ECG signal quality, and chest hair was carefully clipped if necessary. Radiolucent ECG electrodes were applied in the Mason-Likar limb lead configuration so as to not interfere with chest x-rays. During the Holter recording, positional ECGs were obtained with patients assuming supine, right, and left lying positions, which were used during offline analysis to identify false-positive ST-segment changes due to body position changes.[23] The Holter remained in place until discharge from the hospital. All of the patients were also monitored using the hospital's telemetry ECG system as per the hospital's protocol; thus, the standard of care was not interrupted by the research protocol. For this study, all of the patients had at least 8 hours of Holter recording.

A research nurse, present during the hours of 7 AM to 5 PM, made hourly quality checks on the patients enrolled to ensure that the Holter recorder was in place, the ECG electrodes/lead wires had not been removed, and/or the location of the electrodes had not been changed from the correct location. At these inspections, the research nurses also addressed any questions or concern the patient and/or nurse had about the research protocol. This approach meant that reapplication of any electrode(s) that have fallen off or were taken off for procedures was promptly corrected. The research nurse also retrieved demographics, clinical history, procedures (ie, treadmill test, cardiac catheterization laboratory), medications, laboratory values, and outcome data from the electronic health record.

Electrocardiogram Analysis for Identifying Transient Myocardial Ischemia

Data from the Holter recorder were downloaded to a password-protected research computer. The download was done at hospital discharge in patients admitted less than 24 hours or at 24-hour intervals for those admitted longer than 24 hours because the card reader had reached storage capacity. In these patients, a new card reader was replaced immediately in the Holter recorder to ensure that continuous 12-lead ECG data were recorded. The Holter recorder remained on the patient until hospital discharge; the patient asked to have the device removed, which was rare; or the patient went to surgery.

The ECG data were analyzed using the H-Scribe Analysis System (Mortara Instruments, Milwaukee, Wisconsin). The H-Scribe software displays 24 hours of ECG recordings and identifies ST-segment changes that meet the ST-segment threshold criteria for transient myocardial ischemia. We define transient myocardial ischemia using the standard definition of greater than or equal to 1 mm of ST-segment elevation or depression, in 1 or more ECG lead(s), lasting at least 1 minute.[23] The ECG analysis for identifying transient myocardial ischemia was performed using a semiautomated approach. All of the H-Scribe computer software events were overread by the principal investigator (M.M.P.), who carefully examined changes to the ST-segment trend (elevation or depression) during the entire monitoring period in all 12-ECG leads. Twelve-lead ECGs were printed out and compared pre, during, and post ischemia to confirm the diagnosis. The human annotator was blinded to demographics, clinical history, and/or clinical outcomes. In cases where there were questions about whether transient myocardial ischemia was present or absent, 2 coinvestigators from the parent study reviewed the ECG data, and a consensus was reached.[16]

Holter-Derived Respiratory Disturbance Index

Continuous high-resolution 12-lead ECG data were used to generate an HDRDI using the entire length of Holter recording. The HDRDI algorithm was developed by our coauthor, a biomedical engineer (D.W.M.) at the UCSF Center for Physiologic Research. The HDRDI method has been used to screen for OSA, Cheyne-Stokes respirations, and periodic breathing in previously published studies.[17,19] The HDRDI algorithm uses QRS morphology changes, heart rate, and ECG-derived myogram signals that are associated with inspiration and exhalation (ie, tidal volume changes) to generate respirations. When the normal pattern of respirations is

interrupted, for example, during apnea followed by arousal to break the apnea, the associated ECG changes generate an HDRDI event. The algorithm-identified events allow us to calculate the number of HDRDI events per hour, which is used as an equivalent to an apnea-hypopnea index. The Figure is an example of both normal and abnormal breathing events using our algorithm-based approach from 12-lead ECG recordings.

For this study, we selected patients who were screened as having a moderate HDRDI if they exhibited 15 or more events per hour. Moderate HDRDI was selected so that we could make comparisons of our study results with those done in previous studies using this cutoff point.[3,7] The group of NSTE-ACS patients with moderate HDRDI was compared with those without this measure to determine the peak troponin I level (ng/mL) and the presence of transient myocardial ischemia measured from continuous 12-lead Holter recordings.

Diagnosis of Non–ST Elevation Acute Coronary Syndrome

Venous blood samples were obtained in all of the patients per the hospital's protocol to rule in/out NSTE-ACS. Typically, 3 samples were obtained in a patient during the course of an 18- to 24-hour timeframe. The hospital's troponin I test was considered positive for NSTE-ACS if it was greater than 0.04 ng/mL. For this study, we used the highest troponin level, or peak, to compare those with and without a moderate HDRDI.

Statistical Analysis

Data were analyzed using SPSS 27.0 (International Business Machines [IBM] Corporation 2009). Descriptive statistics were used to report demographics, including age, body mass index, gender, and ethnicity. These same statistics were used to examine the clinical history including angina, coronary arterial bypass graft surgery, coronary arterial disease, current smoker, diabetes, ejection fraction, hypertension, percutaneous coronary intervention, and previous myocardial infarction. In addition, we examined blood pressure and heart rate at admission, the number of angina episodes in the last 24 hours, length of hospital stay, and total Holter monitoring time in hours. Values are expressed as means ± standard deviations and percentages. Categorical variables were analyzed using a Pearson χ^2 test, and continuous variables were examined using a Student *t* test. The Student *t* test was used to compare the mean peak troponin I between patients with NTSE-ACS screened with and without moderate HDRDI. A Pearson χ^2 test was used to compare the proportion of patients with and without transient myocardial ischemia by moderate HDRDI group (yes vs no). A *P* value of less than .05 was used as the critical value to determine whether there were statistical differences.

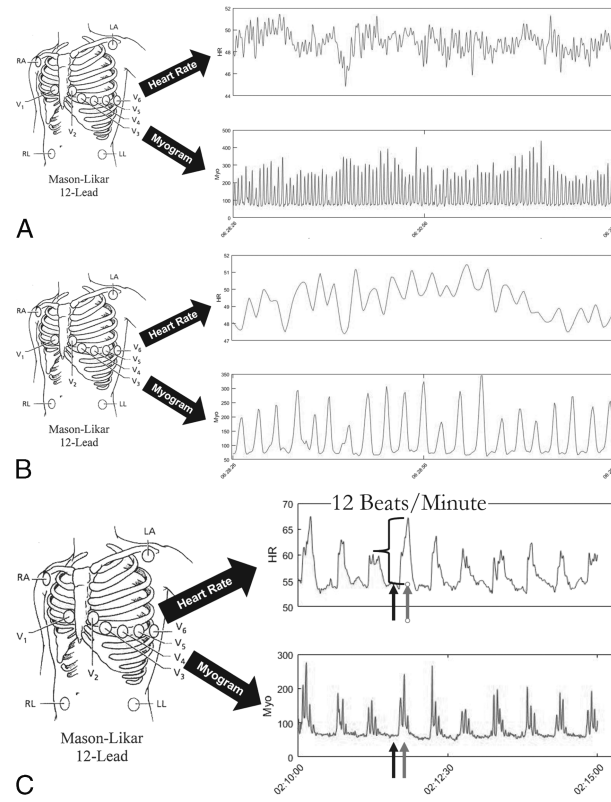

FIGURE. *The 3 images above illustrate Holter-derived respirations from continuous 12-lead electrocardiographic (ECG) recordings. This method uses a combination of QRS complexes, R-to-R intervals, and the myogram (Myo). Images A and B are from a patient during normal breathing, and image C is a different patient with an obstructive breathing pattern (ie, sleep-disordered breathing). A, ECG-derived respiratory rate in a patient breathing normally during a 5-minute period (x-axis). Shown are the trend for heart rate (HR) and Myo. The spikes on Myo correspond to a single breath. B, Same patient shown in A, zooming in on a 1-minute period to illustrate normal breathing at a rate of 21 breaths per minute. C, ECG-derived respiratory rate in a patient with obstructive or sleep-disordered breathing (5 minutes; x-axis). Shown are the trend for HR and Myo. The first arrow denotes when no breathing (apnea) occurs, and the second arrow denotes the clearing of the airway obstruction resulting in a myogram peak and corresponding HR acceleration of 12 beats per minute. Shown are 10 Holter-derived respiratory disturbance index events.*

Results

Table 1 shows the demographic and clinical characteristics, Holter recording time, and hospital length of stay among the 110 patients with NSTE-ACS included in the study. Of the entire sample, 43 (39%) had moderate HDRDI. There was no statistical differences between the groups for age, body mass index, or race. There was a higher proportion of males screened with moderate HDRDI (86% vs 57%; $P = .01$). The opposite was found in females (14% vs 43%; $P = .001$). A higher proportion of patients screened with moderate HDRDI had a history of angina (58% vs 36%; $P = .022$), whereas a lower proportion of patients screened with

TABLE 1 Demographic and Clinical Characteristics of 110 Non–ST Elevation Acute Coronary Syndrome Patients Without and With Moderate Holter-Derived Respiratory Disturbance Index, Suggestive of Sleep-Disordered Breathing (≥15 Events/Hour)

Variable	Entire Sample N = 110 n (%)	No Moderate HDRDI n = 67 (61%) n (%)	Yes Moderate HDRDI n = 43 (39%) n (%)	*P*
Demographics				
Age, mean ± SD, y	65 ± 12	66 ± 13	63 ± 11	.290
BMI, mean ± SD	29.9 ± 5.2	29.7 ± 5.3	30.1 ± 4.9	.731
Sex				
Female	35 (32)	29 (43)	6 (14)	.001
Male	75 (68)	38 (57)	37 (86)	.001
Race				
American Indian or Alaskan Native	3	1 (2)	2 (5)	.524
Black/African American	1	1 (2)	0	
Pacific islander	1	1 (2)	0	
White	105	64 (96)	41 (95)	
Clinical history				
Angina	49 (45)	24 (36)	25 (58)	.022
CABG	22 (20)	14 (21)	8 (19)	.769
CAD	62 (56)	39 (58)	23 (54)	.626
Current smoker	65 (59)	42 (63)	23 (54)	.338
Diabetes	33 (30)	25 (37)	8 (19)	.037
EF	57 ± 11	55 ± 12	58 ± 9	.600
HTN	69 (63)	45 (67)	24 (56)	.230
PCI	41 (37)	29 (43)	12 (28)	.104
Previous MI	40 (36)	27 (40)	13 (30)	.284
Presenting ACS variables				
Admission systolic blood pressure	145 ± 27	142 ± 27	151 ± 25	.076
Admission diastolic blood pressure	84 ± 16	82 ± 17	87 ± 15	.098
Admission heart rate	79 ± 18	82 ± 20	75 ± 13	.026
Presence of 2–3 angina events in the last 24 h	32 (29)	18 (27)	14 (33)	.521
Hospitalization variables				
Average length of hospitalization, h	88 ± 86	95 ± 86	77 ± 86	.278
Total Holter monitoring time, h	37 ± 19	39 ± 21	34 ± 15	.152

Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; EF, ejection fraction; HDRDI, Holter-derived respiratory disturbance index; HTN, hypertension; MI, myocardial infarction; PCI, percutaneous coronary intervention.

moderate HDRDI had diabetes (19% vs 37%; *P* = .037). The other clinical history characteristics were not different by group. Admission blood pressure (systolic and diastolic) and the presence of 2 to 3 angina events in the last 24 hours were not different by group, but patients screened with moderate HDRDI had a lower admission heart rate (75 vs 82 beats/min; *P* = .026). There was no difference between the groups with regard to the length of hospitalization or total Holter recording time.

Table 2 shows group comparisons for peak troponin and transient myocardial ischemia. Patients with NSTE-ACS screened with moderate HDRDI had lower peak troponin levels (6.8 vs 10.2 ng/mL; *P* = .037). There was a trend for a lower proportion of patients with transient myocardial ischemia events screened with moderate HDRDI, but this difference was not statistically significant (16% vs 30%; *P* = .081).

Discussion

This study, in which we examined 110 patients with NSTE-ACS, showed that 39% met our screening criteria for moderate HDRDI identified using continuous 12-lead Holter recordings. Peak troponin was lower in those screened with moderate HDRDI as compared with those who did not meet screening criteria for moderate HDRDI. There was a trend for fewer transient myocardial ischemic events in those screened with moderate HDRDI, but the difference was not statistically different.

The findings from our study with regard to lower peak troponin levels in patients with ACS who screened positive with moderate HDRDI are consistent with 2 previous studies.[7,11] In both studies, peak troponin was obtained in the early phase of ACS (ie, <24 hours). Both studies used similar respiratory polygraphy devices to identify ACS patients with OSA. Shah et al used an apnea-hypopnea index of 5 or greater (mild) and 35% met this criteria, whereas Sánchez-de-la-Torre et al, like in our study, used an apnea-hypopnea index of 15 or greater (moderate). Of note, our rate of HDRDI OSA (39%) was half that reported in the Sánchez-de-la-Torre et al study, which was 70% in their study. Our study used a novel approach to screen for OSA by using 12-lead Holter recordings, but these proportional differences

TABLE 2 Comparison of Peak Troponin and Transient Myocardial Ischemia Among 110 Patients With Non–ST Elevation Acute Coronary Syndrome (Holter-Derived Respiratory Disturbance Index) Was Used to Determine Moderate Sleep-Disordered Breathing (≥15 Events/Hour)

Total N = 110	No Moderate HDRDI n = 67 (61%)	Yes Moderate HDRDI n = 43 (39%)	*P*
Highest troponin I, mean	10.2 ng/mL	6.8 ng/mL	.037
Transient myocardial ischemia	20 (30%)	7 (16%)	.081

Abbreviations: HDRDI, Holter-derived respiratory disturbance index; mL, milliliters; ng, nanogram.

may suggest the ECG-derived method may undercount apnea episodes. Regardless of these differences, our study corroborates the findings that there may be a cardioprotective effect from ischemic precondition in patients with ACS who screened positive for OSA.

Our findings are opposite of those of Barbé and coworkers.[6] In their study, patients with moderate/severe OSA had higher peak troponin levels than those who did not. This might be explained by the sample. Barbé et al included patients with both ST-segment elevation myocardial infarction and NSTE-ACS, whereas our study included only patients with NSTE-ACS. Patients in their study also had respiratory polygraph 48 to 72 hours after admission, which is well past the time when we screened for an HDRDI and was similar to the timeframe of Shah et al and Sánchez-de-la-Torre et al. It is unclear when troponin levels were drawn in the Barbé et al study, but our study used those obtained within 24 hours of admission, which was also done in the Shah et al and Sánchez-de-la-Torre et al studies. Therefore, when troponins were drawn and the diagnosis of OSA was determined during the course of ACS hospitalization may account for study differences.

In an animal study conducted by Murry et al,[8] the investigators showed that intermittent episodes of ischemia did have a cardioprotective effect (ie, ischemic preconditioning) on the myocardium during the early course of ischemia, but this dissipated when ischemia was sustained. Thus, on the basis of these findings, it is unclear whether intermittent hypoxia associated with OSA in the early stages of ACS truly protects the myocardium or only delays more severe myocardial damage. However, whether this finding leads to long-term untoward outcomes is not entirely known.[25] Further studies are needed to better understand these intriguing physiological mechanisms.

Our study went a step beyond previous studies in that we also examined transient myocardial ischemia measured using the noninvasive criterion-standard 12-lead ECG. Two previous hospital-based studies found higher rates of recurrent angina, measured by patient-reported symptoms, in ACS patients with moderate/severe OSA screened for with a questionnaire. Interestingly, they showed that these patients experienced more cardiac events.[13,14] Importantly, published studies show that transient myocardial ischemia is asymptomatic in as many as 70% of patients with ACS[16] measured with continuous ECG recordings; hence, myocardial ischemia may not have been examined in a comprehensive way in the previous 2 cited studies. Overall, 25% of our patients with NSTE-ACS had transient myocardial ischemia, which was much higher than the rate measured by symptoms alone in the aforementioned studies (3.5%,[13] 9.57%[14]). Although we found a lower proportion of patients with transient myocardial ischemia in those screened for moderate HDRDI, this difference was not statistically significant. This is likely due to the small size of our sample but is nonetheless an interesting trend in the same direction as troponin, which should be examined in a future study.

Limitations

Several limitations warrant discussion. One limitation of our study was the use of an ECG-derived method to screen for OSA. However, there have been a number of studies that have evaluated ECG-derived methods to identify abnormal respirations associated with OSA and Cheyne-Stokes respiration.[17–22] In addition, because our method does not measure nasal flow as is used in polygraph testing, we are unable to differentiate obstructive from central sleep apnea. The pathophysiological mechanisms at play between these 2 apnea types (eg, OSA vs central sleep apnea) are important and could have an important impact on the downstream manifestations of these pathologies. We did not obtain whether a patient had a history of OSA during the primary study data collection, which may have been useful for validating OSA using our ECG screening method. Despite these limitations, an ECG screening method for OSA represents an interesting and convenient method for research into the possible mechanisms of OSA during ACS and possibly even a screening instrument, given that ECG monitoring is a standard of care for hospitalized patients with ACS. Continuous ECG data also allows for the examination of other important pathophysiological mechanisms, such as ischemia, heart rate variability, and dysrhythmias, and should be examined in a future study. However, our HDRDI method requires further validation before it can be introduced into clinical care for screening OSA. Finally, our sample was small and only included patients with NSTE-ACS

What's New and Important

- Non–ST elevation ACS patients with moderate OSA, measured with 12-lead Holter recordings, have lower troponin levels than those without moderate OSA.
- The occurrence of transient myocardial ischemia was not different between patients with and without moderate OSA.
- The novel 12-lead ECG method used in this study to screen for OSA in hospitalized patients with ACS may offer the ability to screen patients for OSA but requires further validation against the criterion standard polysomnography.

during a short timeframe after the acute ACS event. Additional studies examining all types of ACS (ie, ST-segment elevation myocardial infarction, NSTE-ACS, unstable angina) that evaluate this phenomenon during the latter part of hospitalization and postdischarge are needed to better understand the physiologic trajectory of ischemia in OSA. The authors of these future studies should also examine transient myocardial ischemia.

Conclusions

Although OSA is associated with a number of cardiovascular complications, including hypertension, atrial fibrillation and other dysrhythmias, heart failure, coronary artery disease, ACS, stroke, diabetes, and cardiovascular mortality,[26] the pathophysiologic mechanisms at play are not entirely understood. Counterintuitively, our findings and others show that peak troponin levels are lower in ACS who screened positive for moderate OSA when measured in the early phase of ACS and may suggest a cardioprotective effect via ischemic preconditioning in patients with ACS who have OSA. However, these findings may not be present in the latter phase of ACS because others investigators have found that myocardial damage eventually occurs. Therefore, myocardial cellular death may only be delayed in ACS patients with OSA. Future research studies in which authors examine the impact of OSA in patients with ACS at both early and late phases in and out of the hospital would help enhance our understanding of the potential role of OSA on the myocardium. Recently published American Heart Association recommendations emphasize the need for OSA screening because this pathology is often unrecognized and thus undertreated in cardiac clinical care.[26] Our novel ECG-derived screening method, or HDRDI, that uses available ECG data in hospitalized patients with ACS might be a potential screening instrument but needs further validation against the criterion-standard polysomnography method.

REFERENCES

1. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. *Circulation*. 2020;141(9):e139–e596. doi:10.1161/CIR.0000000000000757.
2. 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.
3. Sánchez-de-la-Torre M, Campos-Rodriguez F, Barbé F. Obstructive sleep apnoea and cardiovascular disease. *Lancet Respir Med*. 2013;1(1):61–72. doi:10.1016/S2213-2600(12)70051-6.
4. Kuniyoshi FH, Garcia-Touchard A, Gami AS, et al. Day-night variation of acute myocardial infarction in obstructive sleep apnea. *Am Coll Cardiol*. 2008;52(5):343–346. doi:10.1016/j.jacc.2008.04.027.
5. Kohler M, Stradling JR. Mechanisms of vascular damage in obstructive sleep apnea. *Nat Rev Cardiol*. 2010;7(12):677–685. doi:10.1038/nrcardio.2010.145.
6. Barbé F, Sánchez-de-la-Torre A, Abad J, et al. Effect of obstructive sleep apnoea on severity and short-term prognosis of acute coronary syndrome. *Eur Respir J*. 2015;45(2):419–427. doi:10.1183/09031936.00071714.
7. 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.
8. Murry CE, Jennings RB, Reimer KA. Pre-conditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation*. 1986;74(5):1124–1136.
9. Neckar J, Ostadal B, Kolar F. Myocardial infarct size-limiting effect of chronic hypoxia persists for five weeks of normoxic recovery. *Physiol Res*. 2004;53(6):621–628.
10. Zong P, Setty S, Sun W, et al. Intermittent hypoxic training protects canine myocardium from infarction. *Exp Biol Med (Maywood)*. 2004;229(8):806–812.
11. 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.
12. Tomai F, Crea F, Chiariello L, Gioffrè PA. Ischemic preconditioning in humans. *Circulation*. 1999;100(5):559–563. doi:10.1161/01.CIR.100.5.559.
13. Correia LC, Souza AC, Garcia G, et al. Obstructive sleep apnea affects hospital outcomes of patients with non-ST-elevation acute coronary syndromes. *Sleep*. 2012;35(9):1241–1245A. doi:10.5665/sleep.2078.
14. Jesus EV, Dias-Filho EB, Mota Bde M, et al. Suspicion of obstructive sleep apnea by Berlin Questionnaire predicts events in patients with acute coronary syndrome. *Arq Bras Cardiol*. 2010;95(3):313–320. doi:S0066-782X2010005000103.
15. Pelter MM, Loranger D, Kozik TM, Fidler R, Hu X, Carey MG. Unplanned transfer from the telemetry unit to the intensive care unit in hospitalized patients with suspected acute coronary syndrome. *J Electrocardiol*. 2016;49:775–783. doi:10.1016/j.jelectrocard.2016.08.010.
16. Pelter MM, Loranger DL, Kozik TM, et al. Among unstable angina and non-ST-elevation myocardial infarction patients, transient myocardial ischemia and early invasive treatment are predictors of major in-hospital complications. *J Cardiovasc Nurs*. 2016;31(4):E10-9. doi:10.1097/JCN.0000000000000310
17. Haigney M, Zareba W, La Rovere MT, Grasso I, Mortara D, GISSI HF M2Risk Investigators. Assessing the interaction of respiration and heart rate in heart failure and controls using ambulatory Holter recordings. *J Electrocardiol*. 2014;47(6):831–835. doi:10.1016/j.jelectrocard.2014.08.002.
18. Maier C, Wenz H, Dickhaus H. Steps toward subject-specific classification in ECG-based detection of sleep apnea. *Physiol Meas*. 2011;32(11):1807–1819. doi:10.1088/0967-3334/32/11/S07.

19. Tinoco A, Drew BJ, Hu X, Mortara D, Cooper BA, Pelter MM. ECG-derived Cheyne-Stokes respiration and periodic breathing in healthy and hospitalized populations. *Ann Noninvasive Electrocardiol*. 2017;22(6):e12462. doi:10.1111/anec.12462.
20. Tinoco A, Mortara DW, Hu X, Sandoval CP, Pelter MM. ECG derived Cheyne-Stokes respiration and periodic breathing are associated with cardiorespiratory arrest in intensive care unit patients. *Heart Lung*. 2019;48(2):114–120. doi:10.1016/j.hrtlng.2018.09.003.
21. Kwon Y, Misialek JR, Duprez D, et al. Sleep-disordered breathing and electrocardiographic QRS-T angle: the MESA study. *Ann Noninvasive Electrocardiol*. 2018;23(6):e12579. doi:10.1111/anec.12579.
22. Maier C, Dickhaus H. Confounding factors in ECG-based detection of sleep-disordered breathing. *Methods Inf Med*. 2018;57(3):146–151. doi:10.3414/ME17-02-0005.
23. Pelter MM, Kozik TM, Loranger DL, Carey MG. A research method for detecting transient myocardial ischemia in patients with suspected acute coronary syndrome using continuous ST-segment analysis. *J Vis Exp. JoVE*. 2012;(70). doi:10.3791/50124.
24. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *J Am Coll Cardiol*. 2014;64(24):e139–e228. doi:10.1016/j.jacc.2014.09.017.
25. Randerath W, Bonsignore MR, Herkenrath S. Obstructive sleep apnoea in acute coronary syndrome. *Eur Respir Rev*. 2019;28(153):180114. doi:10.1183/16000617.0114-2018.
26. Yeghiazarians Y, Jneid H, Tietjens JR, et al. Obstructive sleep apnea and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2021;144(3):e56–e67. doi:10.1161/CIR.0000000000000988.