Skin sympathetic nerve activity and ST-segment depression in women

Sanjana S. Borle, BS,[*†] Xiao Liu, MD, PhD,[†] Anxhela Kote, BS,[†] Carine Rosenberg, BS,[†] Jewel N. Reaso, BS,[†] Peng-Sheng Chen, MD, FHRS,[†] C. Noel Bairey Merz, MD,[*†] Janet Wei, MD[*†]

*From the *Barbra Streisand Women's Heart Center, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California, and †Department of Cardiology, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California.*

BACKGROUND ST-segment depression (ST depression) on exercise electrocardiogram (ECG) and ambulatory ECG monitoring may occur without myocardial ischemia. The mechanisms of nonischemic ST depression remain poorly understood.

OBJECTIVE The study sought to test the hypothesis that the magnitudes of skin sympathetic nerve activity (SKNA) correlate negatively with the ST-segment height (ST height) in ambulatory participants.

METHODS We used neuECG (simultaneous recording of SKNA and ECG) to measure ambulatory ST height and average SKNA (aSKNA) in 19 healthy women, 6 women with a history of Takotsubo syndrome (TTS), and 4 women with ischemia and no obstructive coronary arteries (INOCA).

RESULTS Baseline aSKNA was similar between healthy women, women with TTS, and women with INOCA (1.098 ± 0.291 μV, 0.980 ± 0.061 μV, and 0.919 ± 0.0397 μV, respectively; $P = .22$). The healthy women had only asymptomatic upsloping ST depression. All participants had a significant ($P < .05$) negative correlation between ST height and aSKNA. Ischemic episodes (n = 15) were identified in 2 TTS and 4 INOCA participants. The ischemic ST depression was associated with increased heart rate and elevated aSKNA compared with baseline. An analysis of SKNA burst patterns at similar heart rates revealed that SKNA total burst area was significantly higher during ischemic episodes than nonischemic episodes (0.301 ± 0.380 μV·s and 0.165 ± 0.205 μV·s; $P = .023$) in both the TTS and INOCA participants.

CONCLUSION Asymptomatic ST depression in ambulatory women is associated with elevated SKNA. Heightened aSKNA is also noted during ischemic ST depression in women with TTS and INOCA. These findings suggest that ST segment depression is a physiological response to heightened sympathetic tone but may be aggravated by myocardial ischemia.

KEYWORDS neuECG; Sympathetic nerve activity; Myocardial ischemia; Exercise testing; Takotsubo syndrome; Ambulatory monitoring; J-wave syndrome

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Introduction

Sympathetic contributions to coronary vasomotor tone may be an important contributor to ischemic heart disease in women who tend to have abnormal coronary vasomotor dysfunction and mental stress–induced ischemia compared with men.[1] Recent studies have demonstrated ischemic ST-segment depression (ST depression) during exercise treadmill testing to be specific for coronary microvascular dysfunction in the absence of obstructive coronary artery disease (CAD),[2,3] while it is generally recognized that ST depression is less specific for ischemia due to obstructive CAD in women than in men.[4] However, there is also a high prevalence of exercise-induced ST depression in asymptomatic women.[5] The mechanisms of nonspecific (nonischemic) ST depression in women remain unclear. It is possible that during daily activity, the changes in autonomic nerve activity may be associated with nonischemic ST depression, which usually manifests as upsloping ST depression caused by downward displacement of the J-wave. Direct recording of the sympathetic nerve activity (SNA) and electrocardiogram (ECG) is needed to determine if elevated SNA is associated with J-point depression.

neuECG is a method to record ECG and skin SNA (SKNA) simultaneously in ambulatory patients.[6] It has been validated by extensive canine and human subject studies.[7,8] Using this method, it is possible to study the relationship between SKNA and ST-segment height (ST height) in ambulatory patients. We performed a prospective ambulatory neuECG study to test the hypothesis that the ST

Address reprint requests and correspondence: Dr Janet Wei, Barbra Streisand Women's Heart Center, Smidt Heart Institute, Cedars-Sinai Medical Center, 127 S. San Vicente Boulevard, Los Angeles, CA 90048. E-mail address: janet.wei@cshs.org.

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KEY FINDINGS

- Asymptomatic ST-segment depression in healthy ambulatory women is associated with elevated skin sympathetic nerve activity.
- Heightened skin sympathetic nerve activity is noted during ischemic ST-segment depression in women with Takotsubo syndrome and ischemia with no obstructive coronary arteries.
- ST-segment depression is a physiological response to heightened sympathetic tone but may be aggravated by myocardial ischemia.

height correlates negatively with the average SKNA (aSKNA) in healthy ambulatory women. We also studied women with a prior history of Takotsubo syndrome (TTS) and those with ischemia with no obstructive coronary arteries (INOCA) to detect ischemic ST-segment changes. We compared the aSKNA between ischemic and nonischemic episodes. The results were used to test the hypothesis that upsloping ST depression in women is a physiological response to heightened sympathetic tone and that ischemic ST depression is associated with further elevated SKNA than nonischemic ST depression in patients with history of TTS and INOCA.

Methods

The institutional review board of the Cedars-Sinai Medical Center approved a prospective observational study of participants undergoing ambulatory monitoring with neuECG. Written informed consent was obtained from all participants before participation. The research reported in this article adhered to the Helsinki declaration. The study participants included healthy women (n = 19), women with a history of TTS and recovered left ventricular ejection fraction (n = 6), and women with stable INOCA who had suspected or confirmed diagnosis of coronary microvascular dysfunction or vasospasm in the setting of no obstructive CAD (n = 4). Healthy women were asymptomatic participants without known cardiovascular diseases and prescription cardiac medications. Among this group, 14 had been used as healthy control subject in another publication, but the ST segment had not been previously analyzed or reported.[9] All participants were provided a commercially available ECG monitor (Bittium Faros 180) (Figure 1A),[8] which was placed vertically on the participant's sternum for continuous ambulatory recording for 7 days. The vertical position was selected to capture a representative inferior ECG lead, given prior data indicating a high prevalence of ischemic ST depressions in the inferior leads (II, III, or aVF) during ambulatory monitoring among women with stable INOCA.[10] Seven participants underwent at least 1 repeat 7-day recording 46 ± 21

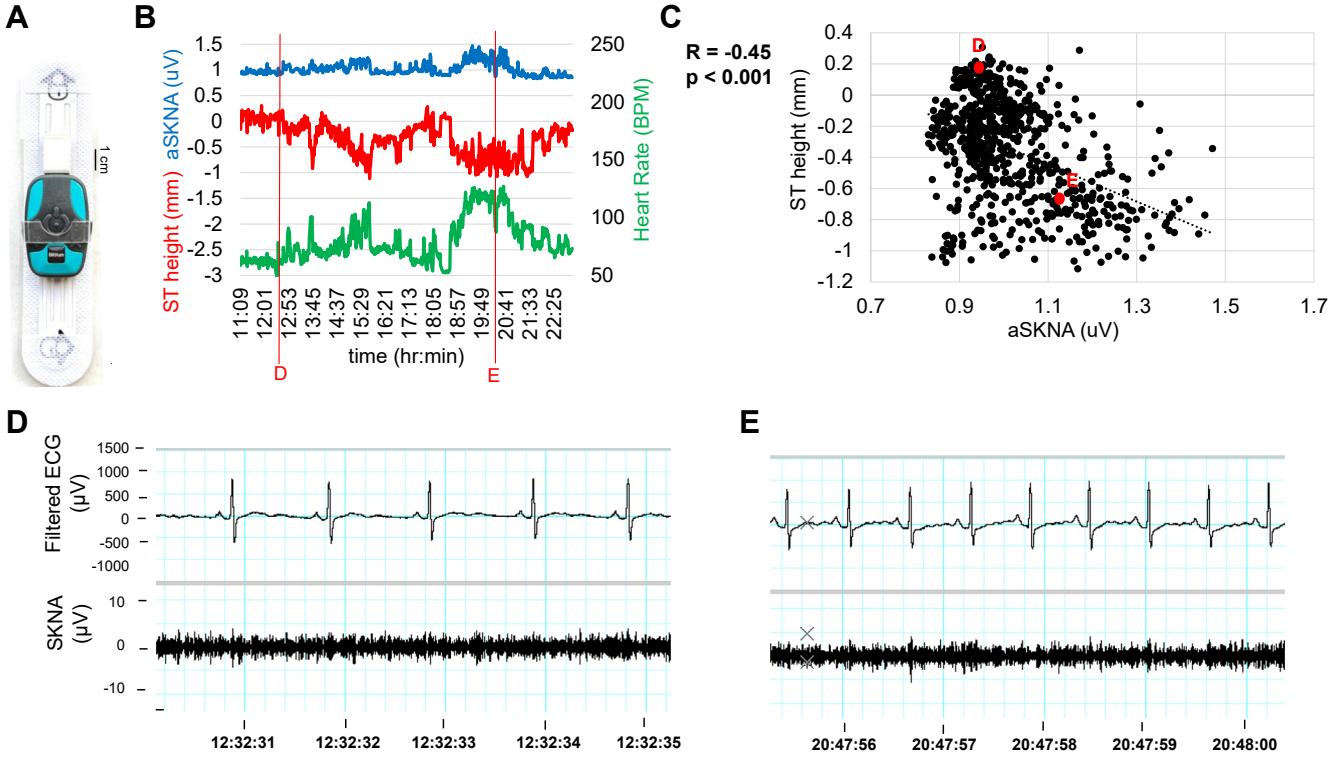

Figure 1 Temporal changes of skin sympathetic nerve activity (SKNA), ST-segment height (ST height), and heart rate (HR) in a 33-year-old healthy female participant. A: The Faros 180 recorder attached to an ePatch. It was placed vertically on the sternum. Numerical values for aSKNA, HR, and ST height values were averaged minute by minute and plotted over the course of an 11-hour recording segment (B). C: Regression between aSKNA and ST height. The original recordings at points D and E on Panels B and C are shown in panels D and E, respectively. No ischemic ST-segment depression was found in this or any other control participants. ECG = electrocardiogram.

Table 1 Participant characteristics, comorbidities, and current medications

	Healthy group (n = 19)	TTS group (n = 6)	INOCA group (n = 4)
Age, y*	30 (20–48)	65 (62–78)	55 (26–77)
Female	19 (100)	6 (100)	4 (100)
Hypertension	0 (0)	4 (67)	2 (50)
Hyperlipidemia	0 (0)	3 (50)	2 (50)
Diabetes	0 (0)	0 (0)	0 (0)
Active smoking	0 (0)	0 (0)	0 (0)
Coronary artery disease	0 (0)	0 (0)	0 (0)
Beta-blocker	0 (0)	1 (17)	2 (50)
Calcium-channel blocker	0 (0)	3 (50)	1 (25)
Nitroglycerin	0 (0)	4 (67)	3 (75)
Statin	0 (0)	2 (33)	1 (25)
Ivabradine	0 (0)	0 (0)	0 (0)
Benzodiazepine	0 (0)	0 (0)	0 (0)
Depression medication	1 (5)	0 (0)	0 (0)

Values are mean (range) or n (%).

INOCA = ischemia with no obstructive coronary arteries; TTS = Takotsubo syndrome.

*$P < .0001$ between groups by analysis of variance.

days later. All medications, including beta-blockers, were continued during testing periods.

Data analyses

Ambulatory ECG and SKNA data were analyzed using the LabChart Pro 8 software (ADInstruments). ECG data were filtered using a band pass of 0.5 to 150 Hz. A template previously established by the neuECG protocol was used to gather filtered SKNA, integrated SKNA, and aSKNA.[8] One-minute averages of ST height, SKNA, and heart rate (HR) were obtained from LabChart and analyzed as discrete data points. ST height was measured by LabChart at 110 ms after the QRS peak. An ischemic episode was defined as at least 30 seconds of horizontal or downsloping ST segment depression $\geq$0.5 mm, when measured 80 ms after the J point. The threshold of $\geq$0.5 mm instead of $\geq$1.0 mm ST-segment depression was used due to prior work demonstrating the prognostic significance of ST-segment depression $\geq$0.5 mm in patients with acute coronary syndromes,[11,12] as well as due to the inclusion of borderline ischemic ECG changes in the evaluation of suspected vasospastic angina.[13] A cardiologist manually verified all ischemic episodes. For ischemia burst analyses, each ischemic episode was also paired with a corresponding control episode. The control episode was defined as a nonischemic episode that occurred within 1 hour of the ischemic episode, and in which the average HR was similar (within 10 beats/min) to the ischemic episode. SKNA data during ischemic episodes were analyzed separately and compared with corresponding control nonischemic episodes using JMP Data Analysis Software (JMP 15.1, SAS Institute Inc., Cary, NC). The software was used to identify the SKNA bursts using previously reported methods.[7] A Microsoft Excel template was used to calculate burst frequency (/min), duration (%), amplitude (μV), and total area above the threshold (μV).[8]

Statistical methods

Pearson regression analyses were performed to assess relationships between SKNA, HR, and ST height variables for each ambulatory recording. Student's t tests assuming unequal variance were used to compare the mean of means between 2 groups of participants, and single-factor analysis of variance tests were used to compare between 3 or more groups. Shapiro-Wilk tests were used to test for normality. Wilcoxon signed rank tests were used to compare the means if the data were not normally distributed. A P value $\leq$.05 was considered significant.

Results

Table 1 shows the participant characteristics, comorbidities, and current medications. All participants in this study were women. Beta-blocker use was more frequent in the INOCA group than the TTS group. Five ischemic episodes were identified in 2 TTS participants, while 15 ischemic episodes were identified in 4 INOCA participants. All ischemic episodes were asymptomatic. The healthy participants did not have any ischemic episodes. The mean aSKNA was 1.088 $\pm$ 0.270 μV for healthy participants, 0.980 $\pm$ 0.061 μV for TTS participants, and 0.919 $\pm$ 0.0397 μV for INOCA participants ($P = .22$). The total duration of recordings was 1380 $\pm$ 120 minutes, 5138 $\pm$ 2434 minutes, and 7201 $\pm$ 1342 minutes for healthy, TTS, and INOCA participants, respectively.

A negative correlation between aSKNA and ST height

We found a significant negative correlation between aSKNA and ST height in all groups. Figure 1 shows an example of upsloping ST depression in a healthy participant. Figure 1A shows the HR, aSKNA, and ST height plotted over time. The HR increased while ST height decreased when aSKNA was increased. There was a significant negative correlation between aSKNA and the ST height (Figure 1B). As expected, the recordings from a healthy participant did not have any ST depression indicating myocardial ischemia either at either low (Figure 1C) or high (Figure 1D) SKNA. For all patients studied, the correlation (r value) between aSKNA and ST height was –0.350 $\pm$ 0.286, while that between HR and ST height was –0.675 $\pm$ 0.222. The P values were $<$.05 for all 19 participants but 1.

Figure 2 shows an example from a TTS participant. Figure 2A shows the changes of aSKNA, HR, and ST height over time. Figure 2B shows a negative correlation between ST height and aSKNA and a positive correlation between HR and SKNA. The original recordings at points C to E in Figure 2B are shown in Figures 2C to 2E, respectively. These graphs show that low aSKNA was associated with normal ST segment (Figure 2C), while heightened aSKNA was associated elevated HR and ischemic ST depression (Figures 2D and 2E). For all patients studied, the correlation (r value) between aSKNA and ST height was –0.287 $\pm$ 0.236, while that

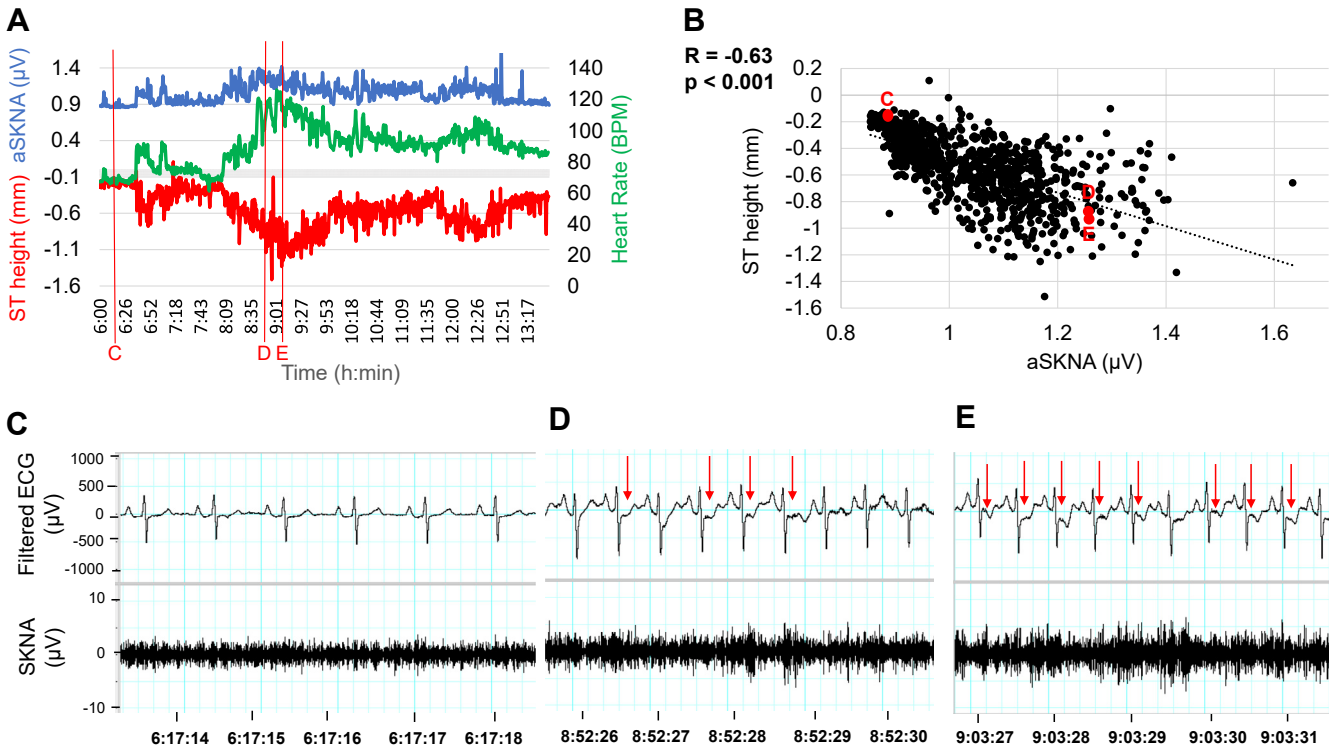

Figure 2 Temporal changes of skin sympathetic nerve activity (SKNA), ST-segment height (ST height), and heart rate (HR) in an ambulatory 78-year-old female participant with a history of Takotsubo syndrome. A 7-hour segment of her recording was analyzed minute by minute for aSKNA, HR, and ST height values. The data were plotted over time, showing that elevated aSKNA is associated with increased HR and depressed ST (A). B: Regression between aSKNA and ST height during this period. The original recordings at points C to E in panel B are shown in panels C to E, respectively. Arrows in panels D and E point to ischemic ST-segment depression, which occurred during heightened SKNA. ECG = electrocardiogram.

between HR and ST height was –0.426 ± 0.273. The *P* values were <.05 for all 6 participants.

Figure 3 shows a similar analysis in an INOCA participant. Figure 3A shows the aSKNA, ST height, and HR over time. Figure 3B shows a strong negative correlation between aSKNA and ST. As in Figure 1, low aSKNA was associated with a normal ST segment (Figure 3C). The ischemic ST depressions were associated with increased HR and elevated aSKNA (Figures 3D and 3E). For all patients studied, the correlation (r value) between aSKNA and ST height was –0.538 ± 0.429, while that between HR and ST height was –0.368 ± 0.481. The *P* values were <.05 for all 4 participants.

Ischemic and nonischemic episodes of similar HR

The difference in SKNA between nonischemic and ischemic episodes at similar HRs was further investigated by conducting a thorough SKNA burst analysis (Figure 4). The ischemic ST depression (Figure 4A) was associated with more frequent SKNA bursts and larger total burst area than the nonischemic episode with similar HR (Figure 4B). We compared the 15 identified ischemic episodes in 6 participants (2 TTS and 4 INOCA) to the 15 nonischemic episodes with similar HR but no ischemic ST depression. The mean SKNA burst areas of ischemic and nonischemic episodes were 0.301 ± 0.38 μV·s and 0.165 ± 0.205 μV·s, respectively (n = 6, *P* = .023 by Wilcoxon signed rank test).

Discussion

There was a significant negative correlation between aSKNA and ST height and a significant positive correlation between aSKNA and HR in all participants. Compared with HR-matched nonischemic episodes, ischemic episodes were associated with larger SKNA burst areas in the INOCA and TTS groups.

Relationship between SKNA and ST depression

We found a negative correlation between aSKNA and ST height in all groups of participants. One potential mechanism for this observation is that sympathetic activity increased HR, which in turn caused repolarization changes that manifested as upsloping ST depression. Indeed, healthy participants only have upsloping ST depressions which are generally considered nonischemic.[14] ST depression occurs when the junction (J) point is displaced below baseline.[14] The J point corresponds to the junction between QRS and ST segment, and its magnitude and timing are determined by the transmural dispersion of the transient outward current (I_{to}). A prominent I_{to}-mediated action potential notch in ventricular epicardium but not in endocardium produces a transmural voltage gradient during early ventricular repolarization that registers as a J-wave or J-point elevation on the ECG.[15] Transient outward channels are subject to α- and β-adrenergic regulation, mainly decreasing I_{to1}.[16] It is possible that elevated SNA suppressed I_{to}, which downwardly displaced

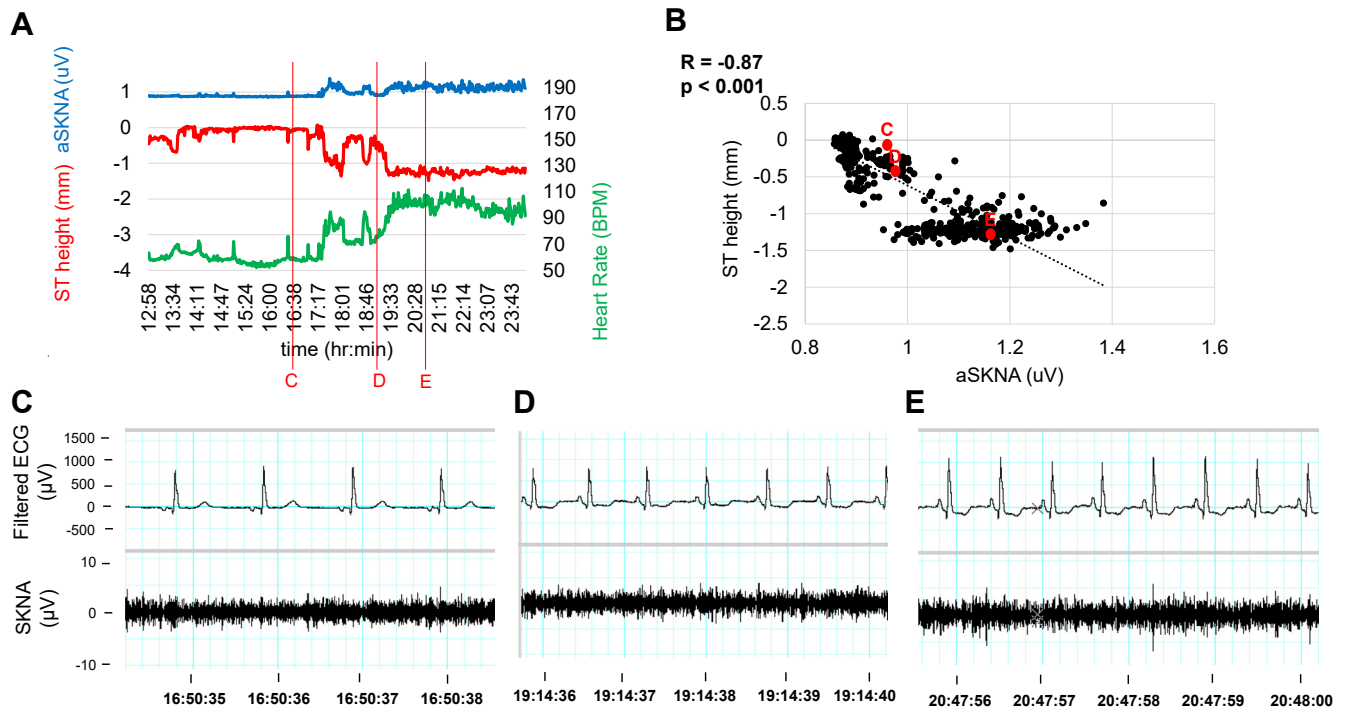

Figure 3 Temporal changes of skin sympathetic nerve activity (SKNA), ST-segment height (ST height), and heart rate in a 63-year-old woman with ischemia with no obstructive coronary arteries. A shows the changes over 11 hours. B: Negative correlation between aSKNA and ST height. The original recordings at points C to E are shown in panels C to E, respectively. C: Absence of ST-segment depression when aSKNA was low. Arrows in panels D and E point to ischemic ST-segment depression, which occurred during heightened aSKNA. ECG = electrocardiogram.

the J point. This could be the mechanism of upsloping ST depression. All our participants were women, who normally have lower magnitudes of I_{to} than men and thus may be more prone to J-point depression during sympathetic stimulation. That may be another reason that prominent upsloping ST depression was observed during SKNA bursts.

ST depression during ischemia

We found a negative correlation between ST height and aSKNA also in patients with TTS and INOCA. Similar to the healthy participants, the majority of the ST depression in these diseased patients occurred in the setting of upsloping ST depression. However, with manual analyses, we were able to find 15 episodes in 6 patients of horizontal or downsloping ST depression that cannot be explained simply by J-point deviation. Those episodes were associated with significantly higher aSKNA levels than HR-matched control nonischemic segments of the same patients. These findings suggest that those horizontal or downsloping ST depression cannot be explained by the HR elevations. Rather, we hypothesize that sympathetic stimulation increased myocardial ischemia, which caused ST depression.

This hypothesis is supported by prior literature evaluating ST depression and HR in patients with suspected INOCA. A previous study showed that atrial pacing alone with rates of 120 to 180 beats/min caused ST depression and/or coronary sinus oxygen desaturation in patients with obstructive CAD or suspected INOCA patients but not in control participants.[17] Similarly, both adrenaline infusion and exercise can cause greater ST depression in INOCA patients compared with control participants despite similar increases in HR.[18] In another study, the ST depression in patients with abnormal ST-T waves at baseline but without obstructive CAD was worsened by the combined use of atrial pacing and adrenaline.[19] Because both adrenaline infusion and exercise activate sympathetic control of coronary vasomotor tone, these mechanistic studies suggest that sympathetic vasomotor tone is the primary determinant of ST depression in patients with pre-existing heart diseases such as TTS and INOCA, although elevated HR could be a contributing factor.

Therapeutic implications

In addition to obstructive CAD, myocardial ischemia can be caused by coronary vasospasm or coronary microvascular dysfunction, namely in patients with INOCA.[20] Microneurography recording of the muscle SNA has demonstrated increased activity during vasospastic angina, suggesting that SNA participates in the pathogenesis of vasospastic angina by enhancing coronary vascular tone.[21] Our findings also offer a mechanism as to why patients with INOCA do respond to beta-blockers clinically.[22] Indeed, ambulatory ischemia has been observed not only in patients with obstructive CAD, but also among those with signs and symptoms of INOCA due to coronary vasospasm and/or microvascular dysfunction.[10] Because ischemic and nonischemic episodes were matched for similar time of day, it is unlikely that circadian variation in ischemic activity would explain these

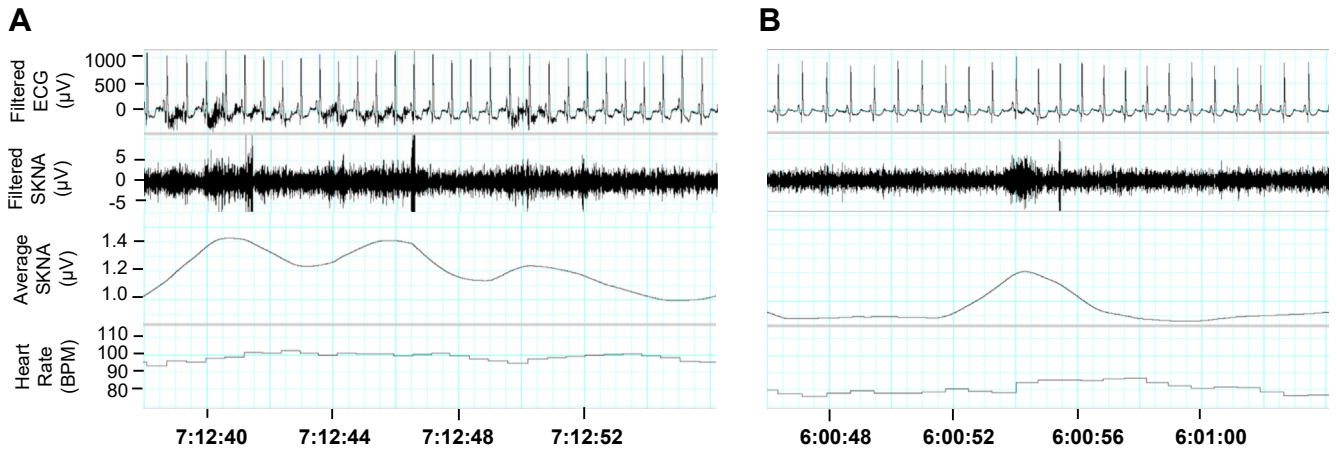

Figure 4 Differences of skin sympathetic nerve activity (SKNA) burst area between ischemic and nonischemic episodes in the same patient. This example was from a 63-year-old woman with ischemia with no obstructive coronary arteries. We first identified an episode with ischemic ST-segment depression (A) with heart rate of 87 ± 9 beats/min. We then reviewed the same recording to find an episode with a similar heart rate 80 ± 3 beats/min but no ischemic ST-segment depression (B). The solid red line on the average SKNA tracings indicates the burst threshold for that episode. The area above the threshold is the burst area. Note that there is a higher burst threshold and larger burst area in ischemic than in nonischemic episodes. ECG = electrocardiogram.

findings.[23] Both TTS and INOCA groups demonstrated an overall increase in total burst area during ischemic episodes, even while most of them were on a beta-blocker as seen in Table 1. This suggests the potential relatively significant effects of autoregulation on ischemic episodes in these patient populations. Previous literature has suggested a future potential for using vagal stimulation to relieve severity of myocardial ischemia, and this study supports the hypothesis that reducing sympathetic activation may be beneficial for reducing myocardial ischemia.[24]

Limitations

Though this study offers promising preliminary results, it has some limitations. We recorded only from the skin, which is well innervated by sympathetic but not parasympathetic nerves. Therefore, the importance of parasympathetic activation on the ST segment could not be evaluated. Because the sample sizes for both TTS and INOCA participants were small, further observational analysis in these populations is warranted to further establish a clear relationship between SNA and ischemia. It is also important to note that in this study participants did not withhold any medications, and these might have affected ambulatory ECG and SKNA readings. Furthermore, ECG recordings were available only in 1 lead, which reduces the sensitivity of ischemia detection; thus, we acknowledge that ST depressions in other leads could have been present in the participants.

Conclusion

Asymptomatic ST depression in ambulatory women is associated with elevated SKNA. Heightened aSKNA is also noted during ischemic ST depression in women with prior TTS and stable INOCA. These findings suggest that ST depression is a physiological response to heightened sympathetic tone but may be aggravated by myocardial ischemia.

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Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: Written informed consent was obtained from all participants before participation.

Ethics Statement: The institutional review board of the Cedars-Sinai Medical Center approved a prospective observational study of participants undergoing ambulatory monitoring with neuECG. The research reported in this paper adhered to the Helsinki Declaration.

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