Characterization of Skin Sympathetic Nerve Activity in Patients with Cardiomyopathy and Ventricular Arrhythmia

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This is the author's manuscript of the article published in final edited form as:
Zhang, P., Liang, J., Cai, C., Tian, Y., Dai, M., Wong, J., … Cha, Y.-M. (2019). Characterization of Skin Sympathetic Nerve Activity in Patients with Cardiomyopathy and Ventricular Arrhythmia. Heart Rhythm. https://doi.org/10.1016/j.hrthm.2019.06.008

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Conflicts of interest: None.

Running title: Skin Sympathetic Nerve Activity and Ventricular Arrhythmia

Word count: 4,639

Funding: This research was funded by the Department of Cardiovascular Medicine, Mayo Clinic (Rochester, Minnesota), NIH grants R01HL134864, R42DA043391, R01HL139829, TR00220, and a Medtronic Zipes Endowment of the Indiana University.

Abstract

Background Heightened sympathetic nerve activity is associated with occurrence of ventricular arrhythmia (VA).

Objective To investigate the association of skin sympathetic nerve activity (SKNA) and VA occurrence.

Methods We prospectively enrolled 65 patients with severe cardiomyopathy. Of these, 39 had recent sustained VA episodes (VA-1 group), 11 had intractable VA undergoing sedation with general anesthesia (VA-2 group), and 15 had no known history of VA (VA-Ctrl group). All patients had simultaneous SKNA and ECG recording. SKNA was assessed using an average value (aSKNA), a variable value (vSKNA), and the number of bursts of SKNA (bSKNA).

Results VA-1 group had higher aSKNA and vSKNA compared with the VA-Ctrl group (aSKNA: 1.41±0.53 vs 0.98±0.41 μV, *P*=.003; vSKNA: 0.52±0.22 vs 0.30±0.16 μV, *P*<.001) and the VA-2 group (aSKNA: 0.83±0.22 μV, *P*<.001; vSKNA: 0.23±0.11 μV; *P*<.001). Although the VA-2 group had more VA episodes than VA-1 group (median, 5 vs 2; *P*=.01), their SKNA was the lowest among the 3 groups. Multivariate Cox regression analysis showed that a higher aSKNA at baseline was an independent predictor of lower VA recurrence rate during a 417±279-day follow-up (hazard ratio, 0.325; 95% CI, 0.119-0.883; P=.03).

A >15% reduction in aSKNA after therapy was associated with a lower subsequent VA event rate (hazard ratio, 0.222; 95% CI, 0.057-0.864; *P*=.03).

Conclusions Patients with VA had increased SKNA as compared with control. Both SKNA and sustained VA could be suppressed by general anesthesia. The aSKNA at baseline was an independent predictor of VA recurrence.

Key words: autonomic nervous system; sedation; skin sympathetic nerve activity; sympathetic tone; ventricular arrhythmia,

Introduction

The autonomic nervous system has an important role in the genesis of cardiac arrhythmias.[1, 2] Sympathetic nerve activity can be recorded by using microneurography techniques, but this approach is invasive and requires technical expertise. Doytchinova et al[3] recently developed a method that uses conventional ECG patch electrodes to noninvasively record skin sympathetic nerve activity (SKNA) simultaneously with electrocardiography (ECG). This new method (neuECG) was used in human studies to show an association between increased SKNA and the onset and termination of paroxysmal atrial fibrillation,[4] premature atrial and ventricular contractions,[5] and ventricular tachyarrhythmia.[3, 6] The noninvasive estimation of sympathetic tone may provide new insights into the mechanisms of cardiac arrhythmias and associated risk factors. It may also provide a measure of the autonomic response to any therapies for arrhythmogenesis. Here, we aimed to study neuECG in patients with cardiomyopathy and sustained ventricular arrhythmia (VA), including ventricular tachycardia and fibrillation. We hypothesized that increased SKNA was associated with ventricular arrhythmogenesis and that the reduced SKNA was predictive of VA recurrence.

Methods

Study Population

We prospectively enrolled 65 patients with structural heart disease and ischemic or nonischemic cardiomyopathy between March 2015 and October 2018, at the Mayo Clinic, Rochester, MN. Subjects at risk of VA were categorized into 3 groups. The VA-1 group consisted of 39 patients with recurrent VA requiring implantable cardioverter-defibrillator (ICD) therapies, and SKNA was recorded while patients were awake. The VA-2 group consisted of 11 patients with recurrent VA requiring ICD therapies who underwent deep sedation with general anesthesia (GA) with intravenous propofol or dexmedetomidine for VA control. The level of sedation was assessed with the Richmond Agitation Sedation Scale (optimal score, −3 or −4). The airway was protected by intubation and ventilation, and SKNA was recorded during sedation with GA. As sedation may impact on the sympathetic activity and VA control, we separated this group (VA-2) from those who did not have sedation (VA-1) for analysis. The VA-Ctrl group consisted of 15 patients without a history of VA who received an ICD for primary prevention of sudden cardiac death.

Data from all VA episodes (including sustained episodes) that occurred before and during the hospitalization were collected by ICD interrogation and telemetry monitoring. A VA storm was defined as 3 or more sustained episodes of VA, or separate appropriate ICD therapies over a 24-hour period.[7] The study protocol was approved by the Institutional Review Boards of Mayo Clinic (Rochester, MN). All

patients have given written informed consent to participate the study.

SKNA Data Acquisition

We used a modified portable ME6000 Biomonitor (Mega Electronics Ltd) for data acquisition. All patients were monitored with ECG leads I and II, with electrodes placed in the right, left subclavian areas and left lower abdomen; another channel was used to record SKNA from the left arm. Data were obtained continuously for 30 to 60 minutes and digitized at 10,000/s. We analyzed recordings from all channels using custom-written software, as described previously.[5] The neuECG signals were amplified and passed through a bandpass filter (30-150 Hz) to display the ECG. The same neuECG signals were passed through another bandpass filter (500-1,000 Hz) to display SKNA.

For quantitative analyses, we reviewed all digitized SKNA signals during a time window and divided the total voltage by the number of digitized samples in the window to obtain the average voltage of SKNA per sample. Neurograms from every 100-millisecond window were rectified and displayed over time to simulate the display methods of microneurography.[3] Data segments with poor signal quality or numerous artifacts were excluded from the analyses. Two investigators independently reviewed the recordings. When discrepancies were identified, the reviewers repeated the data review process together to ascertain the findings.

SKNA Assessment

SKNA was assessed by considering the average voltage of SKNA (aSKNA), a variable value of SKNA (vSKNA), and the number of bursts of SKNA (bSKNA). The aSKNA represents an overall average voltage of SKNA and was obtained by calculating the average value of the continuous monitoring window (60-second window), The bursts of enhanced SKNA (bSKNA) may be transient, in association with temporal clustering VA. bSKNA is quantified by determining the number of enhanced nerve bursts within the first 10 minutes of SKNA data (every 10-second window). The variation of SKNA (vSKNA) may reflect the changes in sympathetic tone and was defined as the standard deviation of aSKNA in every 60-second window. As Kusayama et al[8] described recently, we plotted the proportion of amplitude distribution of SKNA to detect two or more Gaussian distributions. The mean plus 3 times the standard deviation of the first Gaussian distribution was used as the threshold. The nerve activity amplitudes that exceed the threshold were deemed to be in the burst.

Follow-up and Outcomes

Patients were asked to return for a follow-up SKNA assessment at 3 months after hospital discharge. aSKNA was defined as reduced if the voltage was at least 15%

lower than the baseline value. ICD was interrogated to identify any episodes of recurrent sustained VA. The primary end point was recurrent sustained VA requiring ICD therapy (including antitachycardia pacing and shock).

Statistical Analysis

Continuous variables are expressed as mean ± SD. One-way analysis of variance was used to compare the 3 patient groups. Categorical variables are presented as counts and percentages, and groups were compared by using the χ^2 or Fisher exact test, as appropriate. Kaplan-Meier survival curves were generated, and the log-rank test was used to assess differences between curves. In addition, hazard ratios with 95% CIs and *P* values from Cox regression analyses were introduced to identify risk factors of VA recurrence. Two-sided *P* values less than.05 were considered significant. All statistical analyses were performed by using SPSS v.23 (IBM Corporation).

Results

Patient Characteristics

Fifty patients were admitted for VA with appropriate ICD therapies; 39 were in the VA-1 group (13 [33%] with VA storm) and 11 were in the VA-2 group (9 [82%] with VA storm). Fifteen patients without VA were enrolled in the VA-Ctrl group.

The mean ± SD age was 64.0±13.1 years; 52 patients (80%) were men. **Table 1** shows patient baseline characteristics, stratified by VA group.

Ventricular Arrhythmia

Patients in the VA-1 group had a median (range) of 2 (1-112) episodes of sustained VA within 7 days before admission, whereas patients in the VA-2 group had a median (range) of 5 (2-124) episodes (*P*=.01). The median (range) time from last episode of VA to SKNA recording was 2 (1-7) days in VA-1 group, and 1 (1-2) day in VA-2 group (P<.001). Of the 39 patients in the VA-1 group, VA was controlled after receiving antiarrhythmic drugs (AADs, n=38), undergoing catheter ablation (n=17, median time from ablation to SKNA recording 1 (range 1-4) day), or receiving stellate ganglion block (SGB, n=2) following SKNA recording. One patient died of VA and 1 died of cardiogenic shock during hospitalization. Of the 11 patients in VA-2 group, 9 had VA storm, despite receiving AADs. The VA was controlled by sedation with GA (n=11), catheter ablation (n=8, media time from ablation to SKNA recording 1 (range1-7) day, and SGB (n=5, median time to SKNA recording 1(range 1-7) day. Similar to the VA-1 group, 1 patient died of VA and 1 died of cardiogenic shock during hospitalization.

Skin Sympathetic Nerve Activity

The mean±SD neuECG recording time was 50±16 minutes. The aSKNA was higher for the VA-1 group than the VA-2 group (mean±SD, 1.41±0.53 vs 0.83±0.22 μV; *P*<.001) and VA-Ctrl group (0.98±0.41 μV; P=.003) (**Figure 1A**). The vSKNA was substantially higher in the VA-1 group compared with the VA-2 group (0.52±0.22 vs 0.23±0.11 μV; P<.001) and the VA-Ctrl group (0.30±0.16 μV; P<.001) (**Figure 1B**). The bSKNA was higher for the VA-1 group than the VA-2 group (18.30±10.82 vs 7.91±7.06; P=.004), whereas the difference between the VA-1 group and VA-Ctrl group was not significant (**Figure 1C**). Figure 2 shows representative of SKNA tracings from the 3 groups. A patient in the VA-1 group presented with high-amplitude SKNA and a prolonged burst of activity (**Figure 2A**), whereas a patient with VA storm in the VA-2 group had lower-amplitude SKNA and a short burst of activity (**Figure 2B**). A patient in the VA-Ctrl group had intermediate-amplitude SKNA (**Figure 2C**). Within the VA-1 group, the 13 patients with VA storms (33.3%) had a higher vSKNA than those without VA storms (0.61±0.20 vs 0.47±0.21 μV; *P*=.04).

In the VA-2 group, patients did not have recurrence of sustained VA during sedation with GA. **Figure 3A** depicts crescendo bursts of SKNA preceding the episodes of nonsustained VA while the patient was awake (patient with VA storms, VA-2 group). After sedation with GA and AAD therapy, VA and SKNA were suppressed simultaneously **(Figure 3B).** The average amplitude of SKNA was

reduced by 60%.

Predictors of VA Recurrence

A multivariate Cox regression analysis of potential risk factors in the VA-1 group showed that a higher aSKNA at baseline was the only independent predictor of lower VA recurrence rate during a mean follow-up of 417±279 days (hazard ratio, 0.325; 95% CI, 0.119-0.883; P=.03;adjusted for age) (**Table 2**). The VT-2 group was not included in this analysis because SKNA recordings were obtained during sedation with GA. At the 3-month follow-up, 19 patients underwent a repeat SKNA recording. Of these, 11 (57.9%) had recurrent VA during a mean follow-up of 468±268 days. A >15% reduction in aSKNA at 3-month follow-up was associated with a lower subsequent VA event rate compared with those who did not meet this threshold (hazard ratio, 0.222; 95% CI, 0.057-0.864; *P*=.03) (**Figure 4**). VA occurred in only 1 patient with nonischemic cardiomyopathy during follow-up in the control group.

Discussion

This study aimed to determine the association of SKNA with sustained VA events in patients with cardiomyopathy. We had several notable findings: 1) patients with VA had increased aSKNA, vSKNA, and bSKNA; 2) sedation with GA markedly

suppressed VA events and SKNA, and 3) a higher aSKNA at baseline and greater SKNA suppression at the 3-month follow-up were associated with a lower incidence of long-term recurrence rate for VA. Peripheral sympathetic nerve activity can be directly measured with microneurography, [9, 10] but microneurography requires an invasive approach and technical expertise. [4, 5] Our study showed the feasibility of noninvasively measuring SKNA by placing recording patches on the chest and arm and collecting data with the readily available ME6000 device. This approach may be a more convenient method for assessing sympathetic activity than microneurography.

Noninvasive Measurement of Sympathetic Nerve Activity in Patients with VA

The autonomic nervous system regulates cardiac ion channel and myocardial contractility. Elevated sympathetic activity is potentially responsible for initiating VA in patients with or without heart failure.[11] Left stellate ganglion nerve activity (SGNA) dominates cardiac sympathetic control and increases sympathetic output before the onset of VA, and animal models and human studies have shown that inhibition of left stellate ganglion activity reduces the incidence of VA.[12-14] Axonal tracer studies have shown that a considerable portion of skin sympathetic nerves in the neck and upper thorax originate from the ipsilateral stellate ganglion.[15, 16] Subcutaneous nerve activity and superficial SKNA closely correlate with SGNA in

ambulatory canine models.[10, 17, 18] When SKNA and left SGNA were simultaneously recorded continuously in ambulatory canine models, there was a positive correlation between SKNA and SGNA and between SKNA and heart rate, suggesting the SKNA can be used to estimate SGNA.[10]

The findings of elevated aSKNA, vSKNA, and bSKNA in our patients who were hospitalized for recurrent VA events (compared with those who had no known VA documented by ICD) support a model in which VA is associated with heightened sympathetic activity. The periodic crescendo skin nerve bursts that preceded VA episodes in canine models [12] were also observed in patients with VA in our study (when VA episodes were captured).

Sympathetic Suppression and SKNA

VA episodes are associated with various triggers, insults, and underlying severe cardiomyopathy,and incessant, recurrent VA constitutes a medical emergency. Often, medical therapy and catheter ablation fail to control this malignant arrhythmia, and hemodynamic stability is not achieved. A recent study reported that large and sustained sympathetic nerve activity was associated with the temporal clustering of VA episodes, suggesting that neuromodulation methods that inhibit or reduce sympathetic nerve activity may prevent arrhythmia clustering. [8]

Sedation with GA mitigates intractable VA.[19] One of the drug used is dexmedetomidine, which acts in the central nervous system to augment α2 adrenoreceptor restraint on sympathetic nerve activity to multiple tissues and vascular beds. Because of its potent sympatholytic action, dexmedetomidine administration is expected to significantly suppress the sympathetic nerve activity.[20] A previous study used microneurography techniques to show that cocaine increases while dexmedetomidine decreases the skin sympathetic nerve activity, blood pressure and heart rate.[21] In our patients with VA storms, GA plus other concomitant therapies effectively controlled incessant arrhythmia. We observed the measured aSKNA, vSKNA, and bSKNA were lower in the VT-2 group compared with the VT-1 group. This finding is novel because it shows evidence of suppression of sympathetic output by optimal sedation. Although a consensus has not been reached about the optimal level of sedation for treating VA storm, in patients with VA storm associated with hemodynamic instability, sedation with GA and invasive hemodynamic support may be indicated. Others have reported that propofol might be "antiarrhythmic," considering its direct effects on the autonomic nervous system.[22] Notably, 1 of our study patients had SKNA assessment during VA storms in the presedation and postsedation stages. GA markedly suppressed aSKNA, vSKNA, and bSKNA and simultaneously mitigated VA (**Figure 2**).This finding suggests that SKNA may mirror sympathetic

nerve activity in patients with VA and the SKNA recording may provide a feasible measurement when considering stellate ganglion block for VA control.

Implications and Perspective

In this prospective observational study, nearly half the patients had recurrent VA. We noted that patients with a higher aSKNA at baseline and greater reduction of aSKNA at 3-month follow-up were less likely to have subsequent VA episodes. This finding suggests a variation of sympathetic activity in individual patient. The elevated sympathetic output could be arrhythmogenic, associated with VA events and can be reduced by enhanced management of sympathetic control, such as sedation, β-blockers or SGB with a lower likelihood of VA recurrence. On the other hand, a lower sympathetic activity at baseline may suggest a more ventricular substrate-driven, less sympathetic participation in VA occurrence. These findings suggest that sympathetic nerve activity measurement might be used for long term arrhythmic risk assessment in patients with substrates of ventricular arrhythmia.

Study Limitations

Many factors such as age, body mass index, end-stage heart failure, and medication may affect SKNA. We also did not directly record the stellate ganglion nerve activity and correlate it with SKNA. As stated by Shelton et al,[23] the signals of

SKNA may come from multiple sources, although some noise can be effectively filtered with conventional filters. The study was not able to assess the extent of sympathetic activation as we did not measure MSNA or heart rate variability. In addition, this is a prospective observational study. The VA patient grouping without or with sedation was upon physician's discretion with potential patient selection bias. SKNA measures were obtained after sedation for most patients in VA-2 group because of the urgency of VA storm. Therefore, we do not have baseline SKNA measurements for comparison.

Conclusion

SKNA can be feasibly recorded noninvasively. SKNA and VA could be suppressed simultaneously by general anesthesia. Patients with higher SKNA at baseline and reduced SKNA after therapy implies involvement of high sympathetic tone and may have lower recurrence of VA, especially in patients with VA storms.

Acknowledgments

We would like to acknowledge Mrs. Dereen K Ernst for her assistance to the study.

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Figure Legends

Figure 1. Comparison of aSKNA, vSKNA, and bSKNA, Stratified by VA Group.

Patients in the VA-1 group had the highest aSKNA, vSKNA, and bSKNA, whereas patients in the VA-2 group had the lowest aSKNA (A), vSKNA (B), and bSKNA (C).

aSKNA=average value of SKNA; SKNA=skin sympathetic nerve activity; vSKNA=variable value of SKNA; bSKNA=the number of burst of SKNA; VA=ventricular arrhythmia.

Figure 2. Pattern of SKNA in VA-1, VA-2, and VA-Control Groups.

SKNA was characterized by a large and sustained burst in the VA-1 group (A), whereas it was characterized by brief and sporadic bursts in the VA-2 group (B) and VA-Ctrl group (C).

aSKNA=average value of SKNA; ECG=electrocardiogram; SKNA=skin sympathetic nerve activity; VA=ventricular arrhythmia.

Figure 3. SKNA and VA Episodes Suppressed by Sedation.

A, Bursts of SKNA (black arrows) preceded the onset of VA episodes (red arrows) before sedation (aSKNA=1.50 μV). **B**, SKNA and VA episodes were significantly suppressed simultaneously after sedation (aSKNA=0.61 μV). The heart rate decreased from 60 to 50 bpm (blue lines).

aSKNA=average value of SKNA; bpm=beats per minute; ECG=electrocardiogram; HR=heart rate; SKNA=skin sympathetic nerve activity; VA=ventricular arrhythmia.

Figure 4. Repeat aSKNA and VA Recurrence.

Kaplan-Meier curves showed that fewer patients had recurrent sustained VA if they had a >15% reduction in aSKNA compared with those with unreduced aSKNA.

aSKNA=average value of SKNA; SKNA=skin sympathetic nerve activity; VA=ventricular arrhythmia

Figure 1

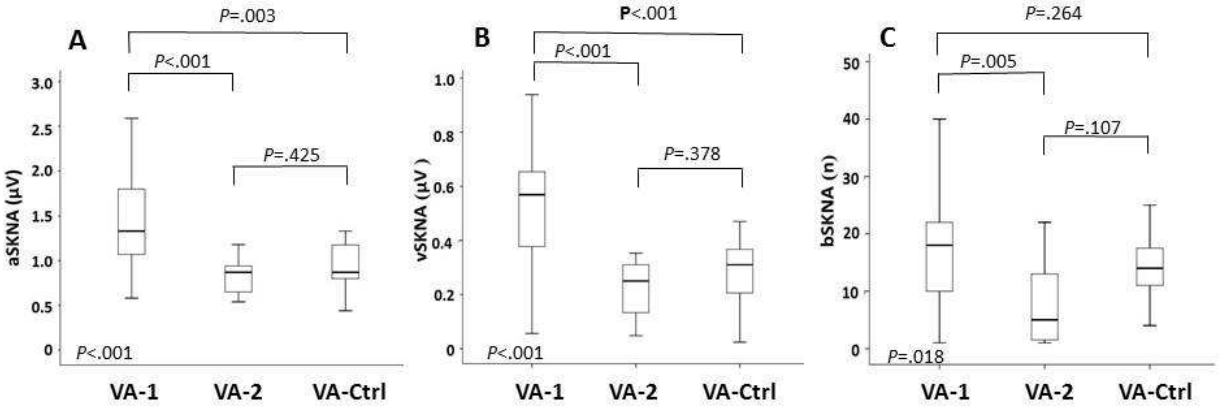


Figure 2

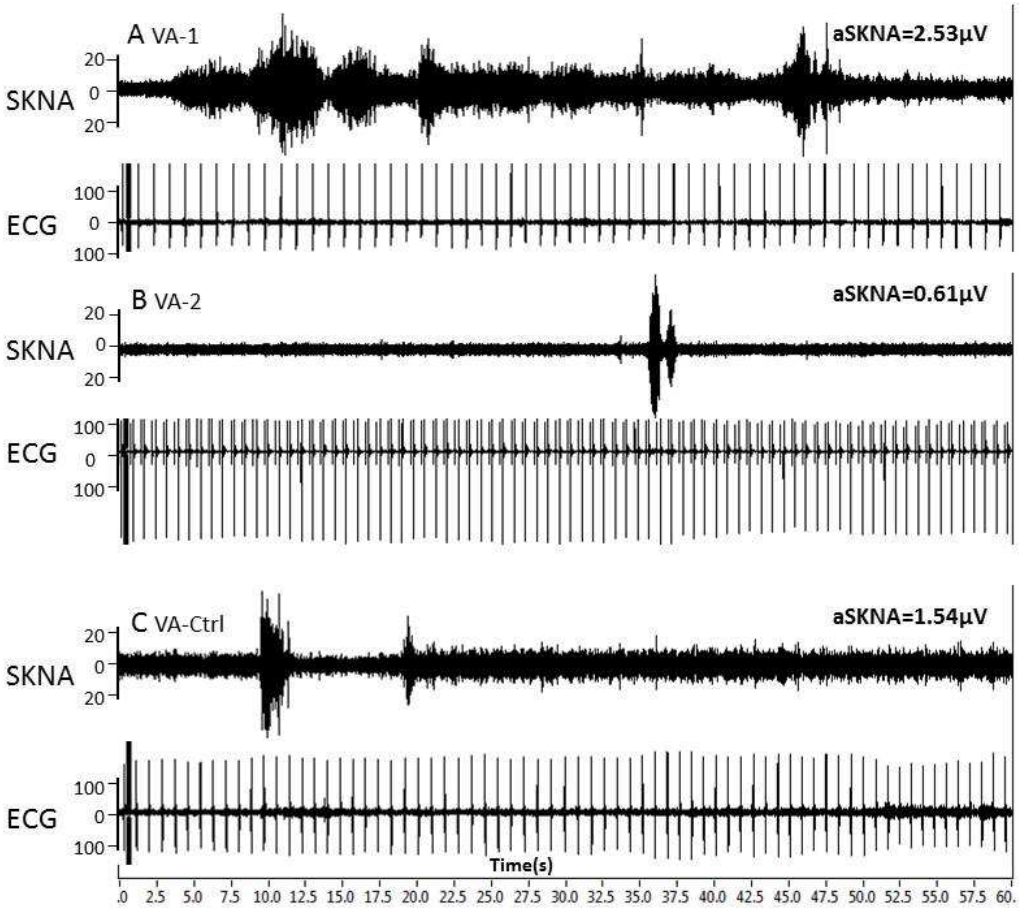


Figure 3

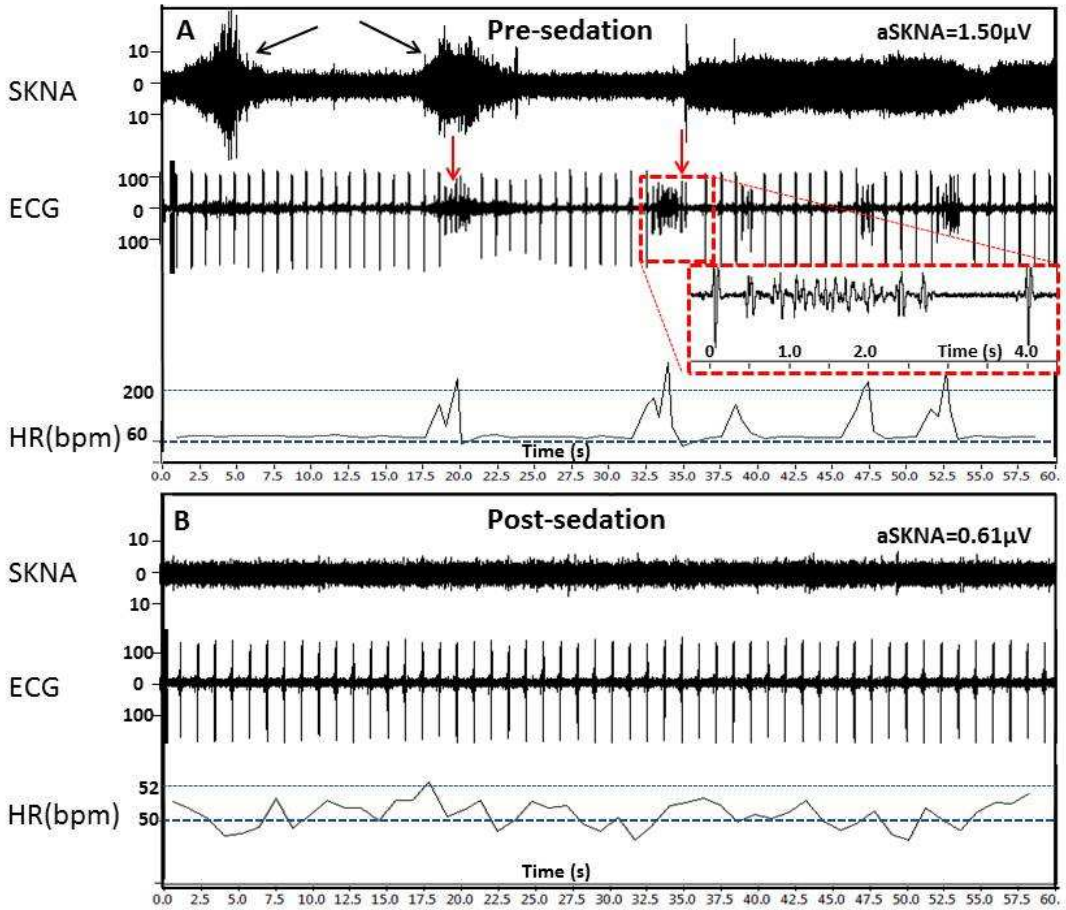


Figure 4

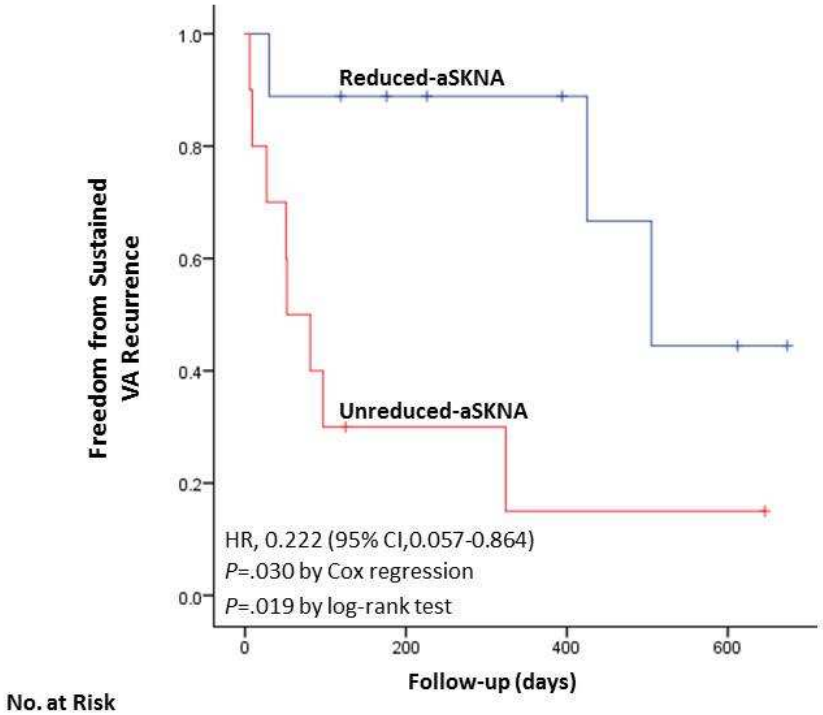


Table 1 Patients Characteristics

Characteristic	VA-1 (n=39)	VA-2 (n=11)	VA-Ctrl (n=15)	*P* Value
Age, (y)	66.1±10.2	58.5±16.2	62.7±16.7	.22
Male, n (%)	35 (89.7)	8 (72.7)	9 (60) *	.03
Body mass index, (kg/m$^{2)}$	32.6±5.6	31.3±5.5	27.4±5.1†	.01
Heart rate, (beats/min)	64.8±9.2	64.5±12.7	67.5±13.0	.58
LVEF, (%)	30.0±10.9	34.3±11.5	26.2±7.8	.15
LVIDd, (mm)	64.5±10.0	58.9±5.2	65.2±8.9	.16
Ischemic heart disease, n (%)	19 (48.7)	6 (54.5)	8 (53.3)	1.0
Diabetes mellitus, n (%)	12 (30.8)	2 (18.2)	4 (26.7)	.86
Hypertension, n (%)	25 (64.1)	3 (27.3)	8 (53.3)	.09
Atrial fibrillation, n (%)	17 (43.6)	3 (27.3)	5 (33.3)	.63
Cardiac resynchronization therapy, n (%)	22 (56.4)	3 (27.3)	3 (20.0) ‡	.04
Sustained VA episodes, median (range ,n)	2 (1-112)	5 (2-124)	…	.01
VA storm, n (%)	13 (33.3)	9 (81.8)	…	.006
AAD, n (%)	32 (82.1)	10 (90.9)	…	1.0
Amiodarone	29 (74.4)	7(63.6)	…	0.75
Mexiletine	8 (20.5)	6 (54.5)	…	0.07

Lidocaine	4 （10.3）	4 （36.4）	…	0.10
ß-blocker, n (%)	35 (89.7)	9 (81.8)	15 (100)	.33
Digoxin, n (%)	3 (7.7)	0 (0)	2 (13.3)	.67
ACEI/ARB, n (%)	30 (76.9)	7 (63.6)	13 (86.7)	.39
Diuretic, n (%)	25 (64.1)	4 (36.4)	10 (66.7)	.26
Aldactone, n (%)	10 (25.6)	5 (45.5)	6 (40.0)	.34

* VA-1 group vs VA-Ctrl group, *P*=.02.

† VA-2 group vs VA-Ctrl group, *P*=.002.

‡ VA-1 group vs VA-Ctrl group, *P*=.03.

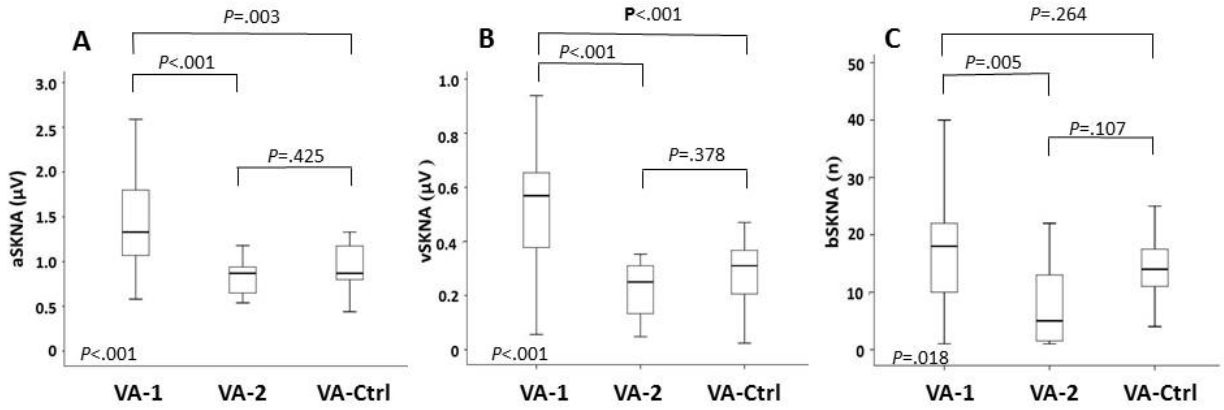
AAD=antiarrhythmic drug, including class I and class III agents; ACEI/ARB=angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers; Ctrl=control; LVEF=left ventricular ejection fraction; LVIDd=left ventricular internal diameter end diastole, VA=ventricular arrhythmia.

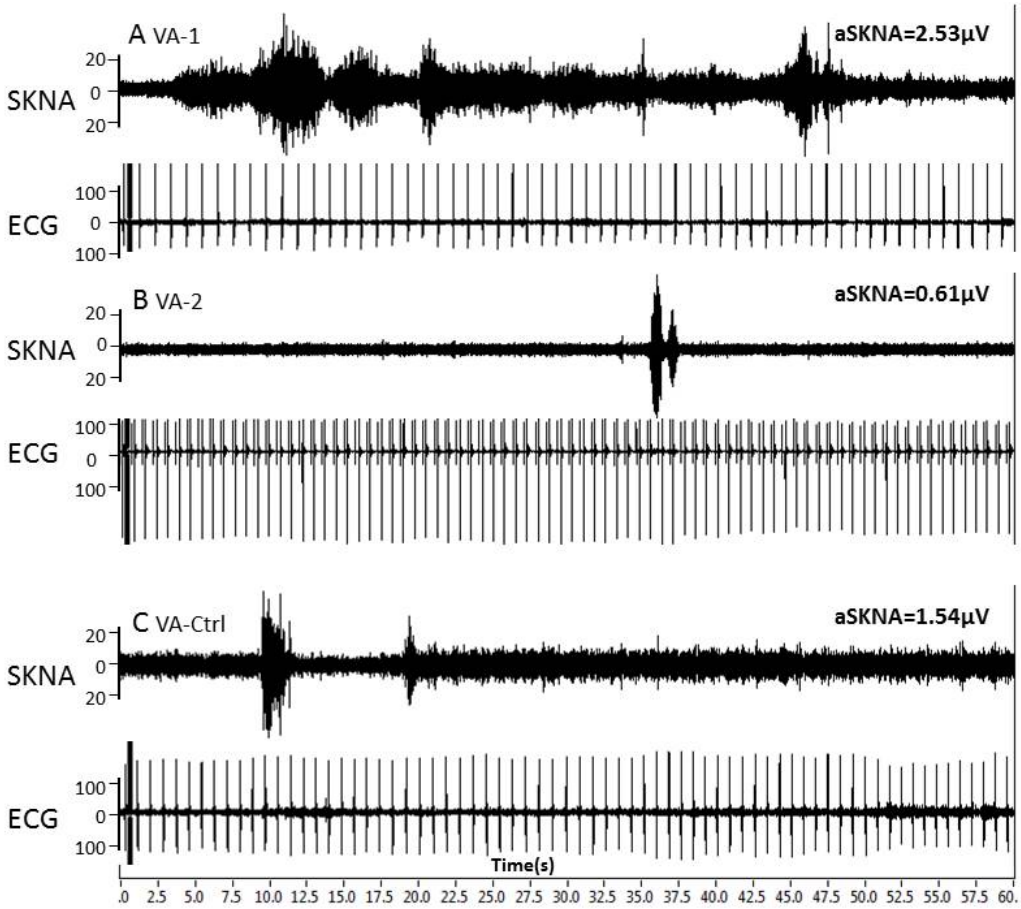
Table 2 Predictors of VA Recurrence in VA-1 Group

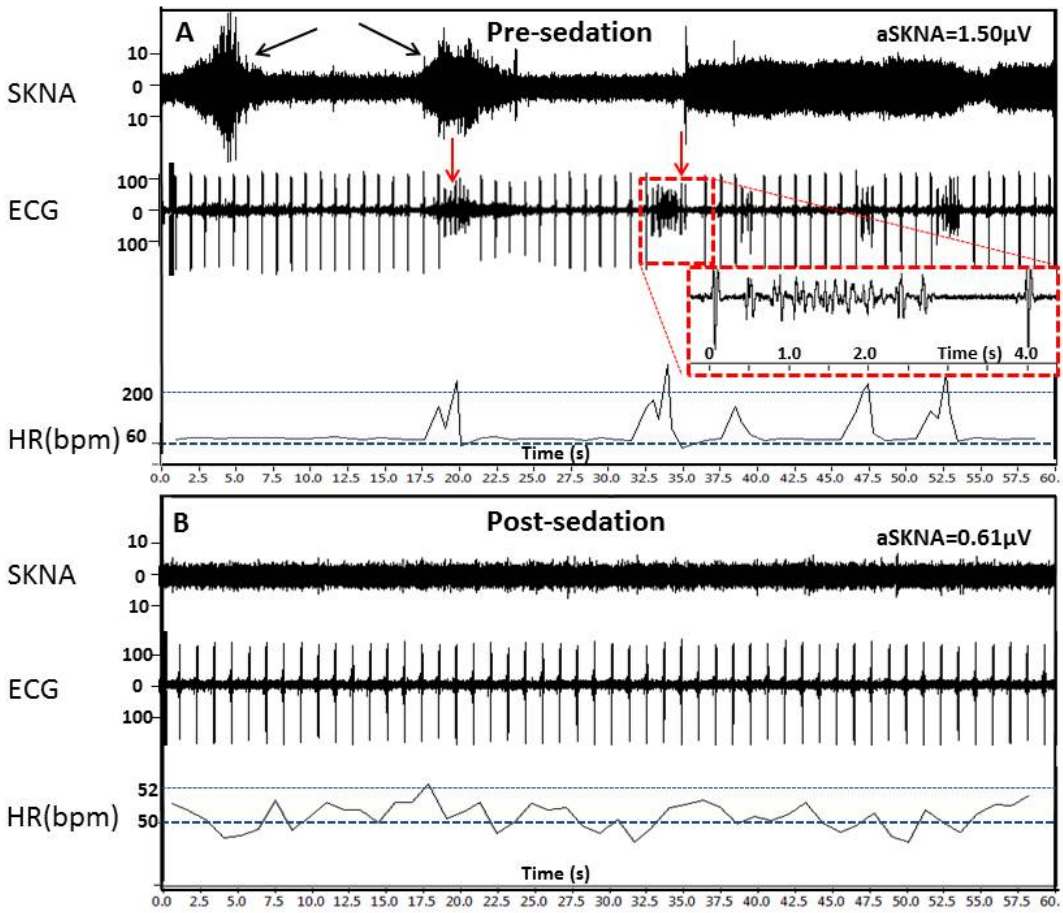
	VA Recurrence (n=18)	No VA (n=21)	Univariate Analysis	
			Hazard Ratio (95% CI)	P Value
Age, (y)	62.4±10.4	69.2±9.1	0.958 (0.916-1.001)	.06
Male, n (%)	18 (100)	17 (81.0)	0.191 (0.010-3.576)	.27
Body mass index, (kg/m^2)	33.6±4.2	31.8±6.5	1.040 (0.959-1.127)	.35
Heart rate, (beats/min)	64.0±8.6	64.6±7.6	0.993 (0.932-1.058)	.83
LVEF, %	29.1±12.0	30.7±10.1	0.984 (0.939-1.031)	.50
LVEDd, (mm)	64.5±9.3	64.6±10.7	1.015 (0.963-1.064)	.63
Ischemic heart disease ,n (%)	7 (38.9)	12 (57.1)	1.889 (0.696-5.123)	.21
Diabetes mellitus, n (%)	7 (38.9)	5 (23.8)	1.531 (0.593-3.952)	.38
Hypertension, n (%)	12 (66.7)	13 (61.9)	0.947 (0.349-2.573)	.92
Atrial fibrillation, n (%)	9 (50.0)	8 (38.1)	2.082 (0.772-5.617)	.15
Cardiac resynchronization therapy, n (%)	8 (44.4)	14 (66.7)	0.871 (0.339-2.236)	.77
Chronic kidney disease, n (%)	3 (16.7)	8 (38.1)	0.501 (0.144-1.738)	.28
VA storm, n (%)	8 (44.4)	5 (23.8)	0.560 (0.217-1.441)	.23
Ablation, n (%)	7 (38.9)	10 (47.6)	1.132 (0.702-1.824)	.61
AAD, n (%)	15 (83.3)	17 (81.0)	1.022 (0.293-3.561)	.97
ß-blocker, n (%)	16 (88.9)	19 (90.5)	0.700 (0.158-3.099)	.64
Digoxin, n (%)	2 (11.1)	1 (4.8)	1.554 (0.352-6.852)	.56
ACEI/ARB, n (%)	14 (77.8)	16 (76.2)	0.778 (0.250-2.421)	.67
Diuretic, n (%)	11 (61.1)	14 (66.7)	1.163 (0.441-3.066)	.76
Aldactone, n (%)	4 (22.2)	6 (28.6)	0.640 (0.209-1.957)	.43
aSKNA, (μV)	1.22±0.47	1.62±0.53	0.293 (0.109-0.785)	.02

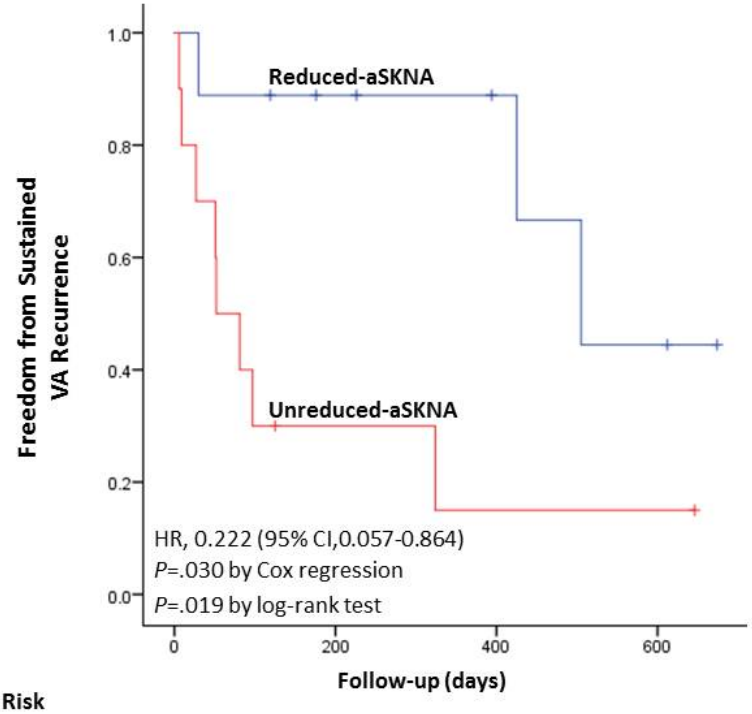
vSKNA, (μV)	0.46±0.23	0.56±0.19	0.998 (0.996-1.000)	.09
bSKNA, (n)	17.9±11.7	17.5±11.4	0.983 (0.937-1.031)	.49

AADs=antiarrhythmic drugs, including class I and class III agents; ACEI/ARB=angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers; LVEF=left ventricular ejection fraction; LVEDD=left ventricular end diastolic diameter; VA=ventricular arrhythmia.


A
P=.003
P<.001
P=.425
P<.001
aSKNA (μV)
3.0
2.5
2.0
1.5
1.0
0.5
0
VA-1
VA-2
VA-Ctrl
B
P<.001
P<.001
P=.378
P<.001
vSKNA (μV)
1.0
0.8
0.6
0.4
0.2
0
VA-1
VA-2
VA-Ctrl
C
P=.264
P=.005
P=.107
P=.018
bSKNA (n)
50
40
30
20
10
0
VA-1
VA-2
VA-Ctrl


A VA-1
aSKNA=2.53μV
SKNA
20
0
20
ECG
100
0
100
B VA-2
aSKNA=0.61μV
SKNA
20
0
20
ECG
100
0
100
C VA-Ctrl
aSKNA=1.54μV
SKNA
20
0
20
ECG
100
0
100
Time(s)
.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0 27.5 30.0 32.5 35.0 37.5 40.0 42.5 45.0 47.5 50.0 52.5 55.0 57.5 60.


A
Pre-sedation
aSKNA=1.50µV
SKNA
ECG
HR(bpm)
Time (s)
B
Post-sedation
aSKNA=0.61µV
SKNA
ECG
HR(bpm)
Time (s)



No. at Risk				
Reduced-aSKNA	9	6	4	2
Unreduced-aSKNA	10	2	1	1