View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by IUPUIScholarWorks

ACCEPTED MANUSCRIPT

Skin Sympathetic Nerve Activity Precedes the Onset and Termination of Paroxysmal Atrial Tachycardia and Fibrillation

First Author's surname: Uradu and Wan

Short Title: SKNA and atrial tachyarrhythmia

Andrea Uradu, MD,[1*] Juyi Wan, MD,[1,4*] Anisiia Doytchinova, MD,[1] Keith C. Wright, MS,[1] Andrew Y.T. Lin, BS,[1] Lan S. Chen, MD,[2] Changyu Shen, PhD,[3] Shien-Fong Lin, PhD, FHRS,[5] Thomas Everett, IV, PhD, FHRS[1] and Peng-Sheng Chen, MD, FHRS[1]

*These two authors contributed equally to this manuscript

Institution: [1]the Krannert Institute of Cardiology, Division of Cardiology, Department of Medicine, and [2]Division of Pediatric Neurology, Department of Neurology, Indiana University School of Medicine, Indianapolis, IN; [3]the Richard and Susan Smith Center for Outcomes Research in Cardiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; [4]Department of Cardiothoracic Surgery, the Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan Province, China and [5]Institute of Biomedical Engineering, National Chiao-Tung University, Hsin-Chu, Taiwan

Address for Correspondence:

Peng-Sheng Chen, MD, 1800 N. Capitol Ave, E475, Indianapolis, IN 46202

Phone: 317-274-0909, Fax: 317-962-0588, Email: chenpp@iu.edu

Total word count: 4976

Disclosures: Shien-Fong Lin and Peng-Sheng Chen have equity interests in Arrhythmotech, LLC.

This is the author's manuscript of the article published in final edited form as:

Uradu, A., Wan, J., Doytchinova, A., Wright, K. C., Lin, A. Y. T., Chen, L. S., … Chen, P.-S. (2017). Skin Sympathetic Nerve Activity Precedes the Onset and Termination of Paroxysmal Atrial Tachycardia and Fibrillation. Heart Rhythm. https://doi.org/10.1016/j.hrthm.2017.03.030

Abstract

Background: Skin sympathetic nerve activity (SKNA) is useful in estimating sympathetic tone in humans

Objective: To test the hypothesis that (1) increased SKNA is associated with the onset and termination of paroxysmal atrial tachycardia (AT) and AF and (2) The sinoatrial node (SAN) response to SKNA is reduced in patients with more frequent of AT or AF.

Methods: SKNA and electrocardiogram were recorded in 11 patients (4 males and 7 females, average age 66±10 years), including 3 patients with AT (11±18 episodes/patient) and 8 patients with AF (24±26 episodes/patient).

Results: The average SKNA (aSKNA, in μV) 10 s prior to AT onset were 1.07±0.10; 10 s after termination were 1.27±0.10, both were significantly ($p=0.032$, $p<0.0001$) higher than that during sinus rhythm (0.97±0.09). The aSKNA 10 s prior to AF onset were 1.34±0.07 and 10 s after termination were 1.31±0.07. Both were significantly ($p<0.0001$) higher than that during sinus rhythm (1.04±0.07). The aSKNA before onset ($p<0.0001$) and after termination ($p= 0.0011$) were both higher in AF than in AT. The sinus rate correlated ($p<0.0001$) with aSKNA in each patient (average r: 0.74, 95% confidence interval (CI): 0.65-0.84). The r in each patient negatively correlated with the number of AT and AF episodes ($r= - 0.6493$, 95% confidence interval:-0.8990 to -0.08073, $p=0.0306$).

Conclusions: Increased SKNA was observed both at onset and termination of AT and AF. The patients with more frequent AT and AF episodes had less of a correlation between sinus rate and aSKNA, suggesting SAN remodeling by tachycardia.

Key words: arrhythmia; autonomic nervous system; cardiac electrophysiology; sick sinus syndrome;

Introduction

It is well documented that the autonomic nervous system plays an important role in arrhythmogenesis in both animal models and in humans.[1, 2] Studies in ambulatory dogs documented an association between stellate ganglion nerve activity (SGNA) and the paroxysmal atrial tachyarrhythmias, including both atrial tachycardia (AT) and atrial fibrillation (AF).[3-5] However, the invasive nature of SGNA monitoring limits its use in humans. The skin of the thorax and upper extremities is well innervated by sympathetic nerves. Tracer studies showed that the somata of these nerves originate in the cervical and stellate ganglia.[6, 7] It is therefore possible that the sympathetic nerve activity recorded from the skin might be used to estimate SGNA. Consistent with the latter hypothesis, we found that subcutaneous nerve activity (SCNA) and surface skin sympathetic nerve activity (SKNA) in ambulatory dogs correlated well with SGNA.[8-10] In addition, SCNA is more effective than heart rate variability in estimating the sympathetic tone.[11] Encouraged by these results, we[12] showed that it is possible to simultaneously record electrocardiogram (ECG) and SKNA using conventional ECG electrodes in humans. The same electrical signal can be filtered between 0.5 Hz and 150 Hz to display ECG, while high pass filtered at 200 Hz or higher to display SKNA. We named this recording method the neuECG because it is a method to simultaneously record neural discharges and ECG. The validity of neuECG recording was supported by the characteristics of nerve discharges recorded during cold water pressor test, Valsalva maneuvers and also by the correlation with heart rate and ventricular arrhythmias. In addition, lidocaine injection into the stellate ganglion abruptly reduced SKNA. The availability of neuECG made it feasible to test the hypothesis that sympathetic nerve activity is a direct trigger of paroxysmal AT and AF episodes in humans. Additionally, sick sinus syndrome is a commonly associated with atria tachyarrhythmias.[13] Because reverse remodeling of sinoatrial node (SAN) function may occur after catheter ablation of AF,[14] AT and AF may play an important role in the pathogenesis of sinus node dysfunction. Abnormal response of superior SAN to sympathetic stimulation is a

characteristic finding in patients with AF and symptomatic bradycardia.[15] Because SKNA can be used to estimate sympathetic tone in humans,[12] increased SKNA should result in a higher heart rate (HR). We hypothesize that the correlation between the average SKNA (aSKNA) and HR would be less in patients with higher frequency of AT and AF compared to those with lower frequency of AT and AF. The purpose of the present study was to test the hypotheses that increased SKNA is associated with the onset of AT and AF in humans, and that the frequency of AT and AF episodes is negatively associated with SAN response to sympathetic tone.

Methods

This research protocol was approved by the Institutional Review Board of the Indiana University School of Medicine. We reviewed the live telemetry recording of the inpatients and prospectively identified 11 patients (6 male, age 46 to 79) with paroxysmal atrial tachyarrhythmia for neuECG recording. Written and informed consent was obtained from each patient.

Continuous neuECG Monitoring

We used a modified portable ME6000 Biomonitor (Mega Electronics Ltd, Finland) for data acquisition.[12] One channel was used to record ECG lead I on the chest with negative and positive electrodes in the right and left subclavian areas, respectively. A second channel was used to record SKNA from the right arm. The signals from neuECG were amplified and bandpass filtered (0.5 Hz-150 Hz) to show ECG. The same signals were bandpass filtered from 500 Hz-1000 Hz to show SKNA. We analyzed recordings from all channels using custom-written software.

Average SKNA and heart rate before onset and after termination of AT and AF

AF was defined by a sudden onset of rapid irregular atrial activations with irregular ventricular responses. AT was defined by a sudden change from sinus rhythm to rapid (> 100 bpm) and

regular narrow QRS tachycardia. All onset and termination of the arrhythmia episodes were spontaneous. To determine the aSKNA and HR before and after termination of AT and AF, all AT and AF episodes lasting at least 10 s and separated by ≥ 10 s were identified. Shorter episodes were not included in the analyses. We integrated all digitized SKNA signals over that time window and divided the total voltage by the number of digitized samples in the same window to obtain the average voltage of aSKNA per sample. So that we can compare SKNA with traditional microneurography tracings,[16] we also integrated SKNA over every 100 ms and plotted the results over time in the figures. The aSKNA and HR 10 s before onset, during the last 10 s of arrhythmia and within 10 s after termination of these AT and AF were analyzed. The frequency of AT or AF episodes were defined by the ratio between total episodes and the duration (hours) monitored.

Statistical analysis

Continuous variables were summarized by mean and standard deviation; categorical variables were summarized by frequency and percentage. Repeated measure ANOVA models were fitted first to perform an overall test to determine if continuous outcomes under different conditions have the same mean values. If the test was significant, paired T test was used to perform post-hoc pairwise comparisons. Pearson correlation coefficient was used to measure linear correlation between continuous variables and Bonferroni correction was used to adjust significance level due to multiple tests. Linear mixed-effects models were used to analyze AT and AF episodes where subjects were treated as the random effect. All 95% confidence intervals are based on normal distributions of the measurements. Two-sided p values ≤0.05 were considered statistically significant.

Results

Patient characteristic

The patient characteristics are shown in Table 1. We have a total of 11 patients, including 4 males and 7 females with an average age of 66±10 years. Among them, 3 patients had AT and 8 patients had AF. None of them had both types of arrhythmias. There were no complications associated with recording.

Average SKNA increases prior to onset and after termination of AT

We manually reviewed 34 episodes of AT in 3 patients (11±18 per patient). Among them, patient #10 had 32 episodes of AT while patients 1 and 4 had one episode each. The AT duration averaged 23.7±18.7 s. **Figure 1** shows 2 episodes of AT from patient #10. Similar to that found in ambulatory dogs,[3, 4] the onset of AT was preceded by increased SKNA (black arrows). In addition, there was a burst of SKNA and transient HR acceleration (by > 10 bpm in 31 and by > 5 bpm in one episode) prior to AT termination (blue arrows). The same phenomenon was not found in the remaining 2 patients (**Figure 2)**. Statistically, the aSKNA (μV) 10 s prior to AT onset was 1.07±0.10, during the final 10 s of AT was 1.20±0.10, 10 s after termination was 1.27±0.10; all were significantly ($p=0.032$, $p<0.0001$, $p<0.0001$, respectively) higher than that during sinus rhythm (0.97±0.09) of the same patients.

Average SKNA increases prior to onset and after termination of AF

There was a total of 188 episodes of AF in 8 patients (24±26 per patient). The AF duration averaged 471.0±886.5 s. SKNA is significantly increased at the onset (**Figure 3**), during the final 10 s and within 10 s after termination of AF (**Figure 4**). In one episode, two beats of premature atrial contractions (PAC) preceded AF onset (**3B**, blue arrows). Statistically, the aSKNA (μV) 10 s prior to the onset was 1.34±0.07, during the final 10 s of AF was 1.29±0. 07, 10 s after termination was 1.31±0.07; all were significantly ($p<0.0001$) higher than that of sinus rhythm (1.04±0.07).

AF is associated with higher average SKNA than AT

We compared the aSKNA and HR during sinus rhythm and all AT and AF episodes 10 s before onset, during final 10 s of the episode, and 10 s after termination (**Figure 5**). The aSKNA associated with arrhythmias were mostly higher than that during sinus rhythm, but there were apparent overlaps of aSKNA associated with sinus rhythm and that with AT or AF. There was no threshold aSKNA above which AT or AF reliably followed. The aSKNA before onset, during the final 10 s and after termination in AF were both significantly higher than that associated with AT episodes ($p<0.0001$, < 0.0001 and $p= 0.0011$, respectively), although large overlaps of aSKNA also existed between these two groups.

Average SKNA and HR vs frequency of atrial tachyarrhythmia

aSKNA and HR positively correlated with each other in all 11 patients ($p<0.0001$, average r: 0.74, 95% CI: 0.65-0.84) (**Figure 6A**). Interestingly, the correlation coefficient of each patient negatively correlated with the number of AT and AF episodes per hour ($r= - 0.6493$, 95% confidence interval:-0.8990 to -0.08073, $p=0.0306$; **Figure 6B**). In other words, the higher the number of AT or AF episodes, the less responsive the SAN is to sympathetic activation. One outlier (black arrow in **6B**) had > 100 short runs of AT but we only included 32 episodes (those lasted 10 s or longer) in this analyses.

Discussion

In this study we demonstrate several findings: (1) Distinct bursts in SKNA are associated with both onset and termination of paroxysmal atrial tachyarrhythmia. (2) aSKNA is increased before onset, during final 10 s and after termination of AF and AT compared to sinus rhythm. (3) aSKNA associated with AF are higher than that associated with AT. (4) aSKNA positively correlates with HR. However, the correlation becomes less strong as the frequency of AF and

AT increases, suggesting the frequency of AF and AT is a major factor responsible for SAN dysfunction.

Autonomic mechanisms of AF onset

The heart is heavily innervated by the autonomic nerves. This includes extrinsic and an intrinsic cardiac nervous system,[17, 18] both of which consists of sympathetic and parasympathetic components and are important in arrhythmogenesis.[1, 2] In ambulatory dogs, both extrinsic and intrinsic cardiac nerve activations frequently precede the onset of spontaneous AT and AF.[3-5] Ablation of the stellate ganglion or the ganglionated plexi (GP) reduced or eliminated these atrial arrhythmias.[4, 19, 20] In humans, unilateral temporary stellate ganglion block might reduce AF inducibility and decrease AF duration.[21] The neural mechanisms of AF is further substantiated by randomized controlled clinical trials that showed pulmonary vein isolation (PVI) plus GP ablation offered a 20-25% higher success rate compared to PVI alone in patients with AF.[22, 23] Another randomized trial showed that botulinum toxin injection in epicardial fat pads can prevent recurrences of AF after cardiac surgery.[24] While epicardial fat pad ablation does not have long-term effects in animal models,[25] the same group of authors have later concluded that extensively ablating LA covering GP areas along with pulmonary vein antrum isolation enhanced the denervation of autonomic nerve system and seemed to improve procedural outcome in patients with AF.[26]

On the other hand a recent study by Driessen et al[27] concluded that GP ablation in addition to PVI and LA lines in patients with advanced AF (defined as persistent AF, enlarged left atria, or previously failed catheter ablation) did not reduce AF recurrence and had increased episodes of AT 12 months after surgery. We propose that there are several possibilities for this discrepancy. First, while important in inducing AF,[5] GP activity may not be important in AF maintenance.[19] Cryoablation of the stellate ganglia and cardiac branches of vagal nerve only prevented paroxysmal AF but not persistent AF in canine models.[28] Therefore, the fact that

Driessen et al recruited patients with advanced (persistent) AF, many with prior failed ablations, may have significant implications on the results of the study. In contrast, Katritsis et al[23] only recruited patients with paroxysmal AF and no prior ablation to the study, thus demonstrated the benefit of GP ablation. Secondly, Driessen et al may have concluded the study too early. In a study that compared PVI and GP ablation vs PVI and linear ablation in persistent AF, statistically significant difference was noted at 3-year follow up, but not at 1-year.[29] The results of Driessen et al also shown a trend towards better outcomes for both paroxysmal and persistent AF at 1 year, but the differences were not statistically significant. It is possible that longer follow up is needed to demonstrate significant differences.

The results of the present study provided further support of the neural mechanisms of AT and AF by directly measuring the sympathetic nerve activity in patients with spontaneous episodes of these arrhythmias. However, in some patients the aSKNA prior to onset of AT/AF overlapped significantly with the range of aSKNA during sinus rhythm. In those patients, the benefit of neuromodulation might be marginal. Further studies are needed to test the hypothesis that SKNA recording might be helpful in selecting patients for neuromodulation procedures.

Bursts of SKNA prior to atrial tachycardia termination

We demonstrated in one patient that all 32 AT episodes were terminated by a burst of SKNA and a brief acceleration of the heart rate. That sequence of events suggest that transient SKNA burst may be important in terminating AT, probably by overdrive suppression of the arrhythmia. In that patient, suppression of sympathetic tone by either drugs or non-pharmaceutical methods may have both antiarrhythmic and proarrhythmic effects. However, that phenomenon was not observed in the other 2 AT patients. The relationship between sympathetic tone and AT onset/termination may vary from patient to patient. Neuromodulation therapy may be beneficial in some patients, but is unlikely to be uniformly successfully in controlling AT and AF. Whether

or not neuECG is helpful in selecting patients for neuromodulation therapy deserves further study.

Sinoatrial node dysfunction secondary to atrial tachyarrhythmia

We found that the aSKNA and HR correlated with each other. However, the correlation coefficients reduced as the frequencies of AT and AF increased. This finding suggests that SAN was remodeled and became less responsive to sympathetic stimulation in patients with more frequent AT and AF episodes. The association between SAN dysfunction and certain cardiac conditions, such as AF or heart failure, has been well described. In a study by Elvan et al,[30] pacing-induced chronic AF (2-6 weeks) induced SAN dysfunction, as evidenced by prolongation of SAN recovery time and decreases in intrinsic heart rates. Similar conclusions have been reported in humans.[31-33] Moreover, it appears that the SAN dysfunction can be reversed after AF ablation.[14] Acceleration of the calcium clock in the superior SAN plays an important role in sinus rate acceleration during beta-adrenergic stimulation.[34] Abnormal responses of superior SAN to sympathetic stimulation is a characteristic finding in patients with AF and symptomatic bradycardia.[15] Our results suggest that frequent tachyarrhythmia episodes may have remodeled the superior SAN and reduced the calcium clock response during sympathetic stimulation. Another implication is that the relationship between aSKNA and HR may be an indication of the AT and AF burden; a low r value suggests a high AF or AT burden.

Limitations of the study

Because the skin does not have parasympathetic nerves, SKNA can be used to specifically measure sympathetic but not parasympathetic tone. Our data could not be used to test the hypothesis that simultaneous sympathovagal discharges are often needed to induce AT and AF.[4] An important new observation was that a burst of SKNA can accelerate AT rate, leading to AT termination. However, we only have one patient with that observation. It is not possible to

generalize these results to other AT patients. We do not have data in this study to determine if SKNA is causally related to AT/AF onset or termination. Due to the limitation of the equipment, we were limited to study hospitalized patients. These patients may not be representative of all patients with AT/AF. The study was not done during drug-free state, and the drugs can affect the results of the study. The same size is small, thus prevented effective subgroup analyses.

Conclusions

We conclude that increased SKNA is associated with both the onset and termination of AT and AF. The patients with more AT and AF episodes had less of a correlation between sinus rate and aSKNA, suggesting SAN remodeling by tachycardia episodes. These findings also suggest that SKAN may be a useful non-invasive tool in studying the neural mechanisms of cardiac arrhythmia.

Acknowledgements

Supported by a fellowship award from the American Heart Association (Dr Doytchinova), NIH grants R41 HL124741, R42 DA043391 (Dr Everett), P01 HL78931, R01 HL71140 (Dr Chen), a Charles Fisch Cardiovascular Research Award endowed by Dr Suzanne B. Knoebel of the Krannert Institute of Cardiology (Dr Everett), a Medtronic-Zipes Endowment and the Indiana University Health-Indiana University School of Medicine Strategic Research Initiative (Dr Chen). We thank Roxanne Kovacs, RN, MSN for her assistance.

ACCEPTED MANUSCRIPT

References

1. Shen MJ, Zipes DP. Role of the autonomic nervous system in modulating cardiac arrhythmias. Circ Res 2014;114:1004-1021.

2. Chen PS, Chen LS, Fishbein MC, Lin SF, Nattel S. Role of the autonomic nervous system in atrial fibrillation: pathophysiology and therapy. Circ Res 2014;114:1500-1515.

3. Ogawa M, Zhou S, Tan AY, Song J, Gholmieh G, Fishbein MCLH, Siegel RJ, Karagueuzian HS, Chen LS, Lin SF, Chen PS. Left stellate ganglion and vagal nerve activity and cardiac arrhythmias in ambulatory dogs with pacing-induced congestive heart failure. J Am Coll Cardiol 2007;50:335-343.

4. Chou CC, Nguyen BL, Tan AY, Chang PC, Lee HL, Lin FC, Yeh SJ, Fishbein MC, Lin SF, Wu D, Wen MS, Chen PS. Intracellular calcium dynamics and acetylcholine-induced triggered activity in the pulmonary veins of dogs with pacing-induced heart failure. Heart Rhythm 2008;5:1170-1177.

5. Choi EK, Shen MJ, Han S, Kim D, Hwang S, Sayfo S, Piccirillo G, Frick K, Fishbein MC, Hwang C, Lin SF, Chen PS. Intrinsic cardiac nerve activity and paroxysmal atrial tachyarrhythmia in ambulatory dogs. Circulation 2010;121:2615-2623.

6. Donadio V, Nolano M, Provitera V, Stancanelli A, Lullo F, Liguori R, Santoro L. Skin sympathetic adrenergic innervation: an immunofluorescence confocal study. Ann Neurol 2006;59:376-381.

7. Taniguchi T, Morimoto M, Taniguchi Y, Takasaki M, Totoki T. Cutaneous distribution of sympathetic postganglionic fibers from stellate ganglion: A retrograde axonal tracing study using wheat germ agglutinin conjugated with horseradish peroxidase. J Anesth 1994;8:441-449.

8. Robinson EA, Rhee KS, Doytchinova A, et al. Estimating sympathetic tone by recording subcutaneous nerve activity in ambulatory dogs. J Cardiovasc Electrophysiol 2015;26:70-78.

9. Doytchinova A, Patel J, Zhou S, Chen H, Lin S-F, Shen C, Everett IV TH, Lin SF, Chen P-S. Subcutaneous nerve activity and spontaneous ventricular arrhythmias in ambulatory dogs. Heart Rhythm 2015;122:612-620.

10. Jiang Z, Zhao Y, Doytchinova A, et al. Using skin sympathetic nerve activity to estimate stellate ganglion nerve activity in dogs. Heart Rhythm 2015;12:1324-1332.

11. Chan YH, Tsai WC, Shen C, Han S, Chen LS, Lin SF, Chen PS. Subcutaneous nerve activity is more accurate than heart rate variability in estimating cardiac sympathetic tone in ambulatory dogs with myocardial infarction. Heart Rhythm 2015;12:1619-1627.

12. Doytchinova A, J. H, Y. Y, et al. Simultaneous non-Invasive Recording of skin sympathetic nerve activity and electrocardiogram. Heart Rhythm 2017;14:25-33.

13. John RM, Kumar S. Sinus Node and Atrial Arrhythmias. Circulation 2016;133:1892-1900.

14. Hocini M, Sanders P, Deisenhofer I, et al. Reverse remodeling of sinus node function after catheter ablation of atrial fibrillation in patients with prolonged sinus pauses. Circulation 2003;108:1172-1175.

15. Joung B, Hwang HJ, Pak HN, Lee MH, Shen C, Lin SF, Chen PS. Abnormal response of superior sinoatrial node to sympathetic stimulation is a characteristic finding in patients with atrial fibrillation and symptomatic bradycardia. Circ Arrhythm Electrophysiol 2011;4:799-807.

16. White DW, Shoemaker JK, Raven PB. Methods and considerations for the analysis and standardization of assessing muscle sympathetic nerve activity in humans. Auton Neurosci 2015;193:12-21.

17. Armour JA, Murphy DA, Yuan BX, Macdonald S, Hopkins DA. Gross and microscopic anatomy of the human intrinsic cardiac nervous system. Anat Rec 1997;247:289-298.

18. Ardell JL. The cardiac neuronal hierarchy and susceptibility to arrhythmias. Heart Rhythm 2011;8:590-591.

19. Zhao Y, Jiang Z, Tsai WC, Yuan Y, Chinda K, Choi EK, Fishbein MC, Lin SF, Chen PS, Everett THt. Ganglionated plexi and ligament of Marshall ablation reduces atrial vulnerability and causes stellate ganglion remodeling in ambulatory dogs. Heart Rhythm 2016;13:2083-2090.

20. Ogawa M, Tan AY, Song J, Kobayashi K, Fishbein MC, Lin SF, Chen LS, Chen PS. Cryoablation of stellate ganglia and atrial arrhythmia in ambulatory dogs with pacing-induced heart failure. Heart Rhythm 2009;6:1772-1779.

21. Leftheriotis D, Flevari P, Kossyvakis C, Katsaras D, Batistaki C, Arvaniti C, Giannopoulos G, Deftereos S, Kostopanagiotou G, Lekakis I. Acute effects of unilateral, temporary stellate ganglion block on human atrial electrophysiologic properties and atrial fibrillation inducibility. Heart Rhythm 2016.

22. Katritsis DG, Giazitzoglou E, Zografos T, Pokushalov E, Po SS, Camm AJ. Rapid Pulmonary Vein Isolation Combined with Autonomic Ganglia Modification: A Randomized Study. Heart Rhythm 2010;8:672-678.

23. Katritsis DG, Pokushalov E, Romanov A, Giazitzoglou E, Siontis GC, Po SS, Camm AJ, Ioannidis JP. Autonomic Denervation Added to Pulmonary Vein Isolation for Paroxysmal Atrial Fibrillation: A Randomized Clinical Trial. J Am Coll Cardiol 2013;62:2318-2325.

24. Pokushalov E, Kozlov B, Romanov A, et al. Botulinum toxin injection in epicardial fat pads can prevent recurrences of atrial fibrillation after cardiac surgery: results of a randomized pilot study. J Am Coll Cardiol 2014;64:628-629.

25. Oh S, Zhang Y, Bibevski S, Marrouche NF, Natale A, Mazgalev TN. Vagal denervation and atrial fibrillation inducibility: epicardial fat pad ablation does not have long-term effects. Heart Rhythm 2006;3:701-708.

26. Higuchi K, Akkaya M, Koopmann M, Blauer JJ, Burgon NS, Damal K, Ranjan R, Kholmovski E, Macleod RS, Marrouche NF. The effect of fat pad modification during

ablation of atrial fibrillation: late gadolinium enhancement MRI analysis. Pacing Clin Electrophysiol 2013;36:467-476.

27. Driessen AH, Berger WR, Krul SP, van den Berg NW, Neefs J, Piersma FR, Chan Pin Yin DR, de Jong JS, van Boven WP, de Groot JR. Ganglion Plexus Ablation in Advanced Atrial Fibrillation: The AFACT Study. J Am Coll Cardiol 2016;68:1155-1165.

28. Tan AY, Zhou S, Ogawa M, Song J, Chu M, Li H, Fishbein MC, Lin SF, Chen LS, Chen PS. Neural mechanisms of paroxysmal atrial fibrillation and paroxysmal atrial tachycardia in ambulatory canines. Circulation 2008;118:916-925.

29. Pokushalov E, Romanov A, Katritsis DG, Artyomenko S, Shirokova N, Karaskov A, Mittal S, Steinberg JS. Ganglionated plexus ablation vs linear ablation in patients undergoing pulmonary vein isolation for persistent/long-standing persistent atrial fibrillation: a randomized comparison. Heart Rhythm 2013;10:1280-1286.

30. Elvan A, Wylie K, Zipes DP. Pacing-induced chronic atrial fibrillation impairs sinus node function in dogs--electrophysiological remodeling. Circulation 1996;94:2953-2960.

31. Sparks PB, Jayaprakash S, Vohra JK, Kalman JM. Electrical remodeling of the atria associated with paroxysmal and chronic atrial flutter. Circulation 2000;102:1807-1813.

32. Van Den Berg MP, Van GI. Atrial fibrillation and sinus node dysfunction. J Am Coll Cardiol 2001;38:1585-1586.

33. Hadian D, Zipes DP, Olgin JE, Miller JM. Short-term rapid atrial pacing produces electrical remodeling of sinus node function in humans. J Cardiovasc Electrophysiol 2002;13:584-586.

34. Joung B, Tang L, Maruyama M, Han S, Chen Z, Stucky M, Jones LR, Fishbein MC, Weiss JN, Chen PS, Lin SF. Intracellular calcium dynamics and acceleration of sinus rhythm by beta-adrenergic stimulation. Circulation 2009;119:788-796.

ACCEPTED MANUSCRIPT

1

ACCEPTED MANUSCRIPT

Table 1. Patient characteristics

#	Age	Gender	Diagnoses	CHA2DS2-VASc score	Antiarrhythmic medications
1	63	Female	Hyperlipidemia Hypertension	2	Metoprolol
2	46	Female	End-stage kidney disease Diabetes Hypertension Hyperlipidemia	3	Metoprolol
3	65	Female	Lung transplant Diastolic heart failure	3	Amiodarone Metoprolol
4	59	Male	Hypertension Hyperlipidemia Lung transplant	1	Amiodarone Metoprolol
5	74	Female	Diastolic heart failure Metastatic renal cell carcinoma	3	Metoprolol
6	79	Female	Coronary artery disease Coronary artery bypass grafting Hyperlipidemia Hypertension	4	Amiodarone Metoprolol
7	58	Male	Aortic dilation Aortic valve replacement	1	Amiodarone
8	74	Male	Coronary artery disease Severe aortic stenosis	3	Metoprolol

			Diabetes Hypertension		
9	68	Male	Coronary artery disease Myocardial infarction Abdominal aortic aneurysm Hypertension Hyperlipidemia Factor V Leiden deficiency.	4	Amiodarone Metoprolol Verapamil
10	66	Female	Hypertension Diabetes End stage kidney disease	4	Metoprolol
11	78	Female	Coronary Artery Disease Coronary Artery Bypass Heart Failure Mitral valve replacement Tricuspid valve replacement Chronic Kidney Disease Chronic Anemia	6	Carvedilol

1

2

3

ACCEPTED MANUSCRIPT

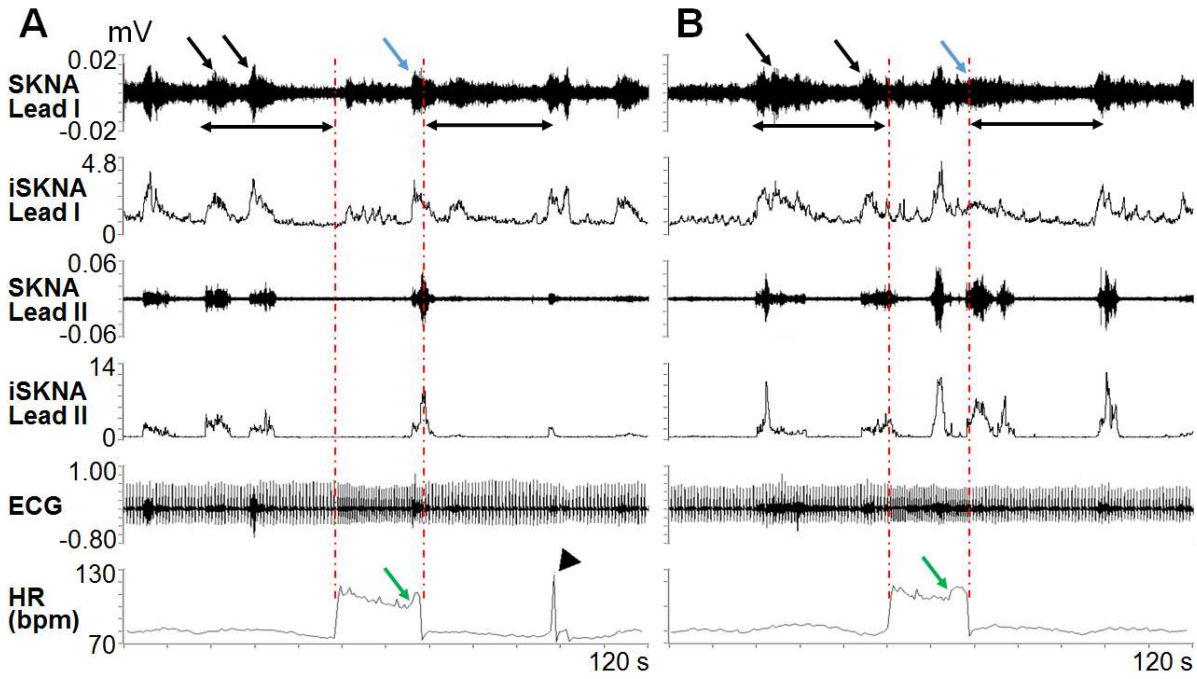

Figure 1. SKNA characteristics before onset and after termination of AT in patient #10, who has 32 episodes of AT fulfilling the inclusion criteria. Signals were high bandpass filtered from 500 Hz-1000 Hz to reveal SKNA and from 0.5 Hz-150 Hz to reveal ECG. iSKNA was obtained by integrating the voltage of digitized data over 100 ms windows. **(A)** Multiple episodes of SKNA bursts (black arrows) were present within 30 s (double headed arrows) prior to AT onset. Heart rate acceleration (green arrows) associated with SKNA burst (blue arrows) was observed prior to AT termination (red dotted line). This phenomenon was present in all 32 AT termination episodes analyzed for this patient. SKNA continues to be elevated during the 30 s after termination. SKNA was also increased during premature atrial contraction (arrowhead). **(B)** Similar findings in a separate AT episode, consistent with (A).

ACCEPTED MANUSCRIPT

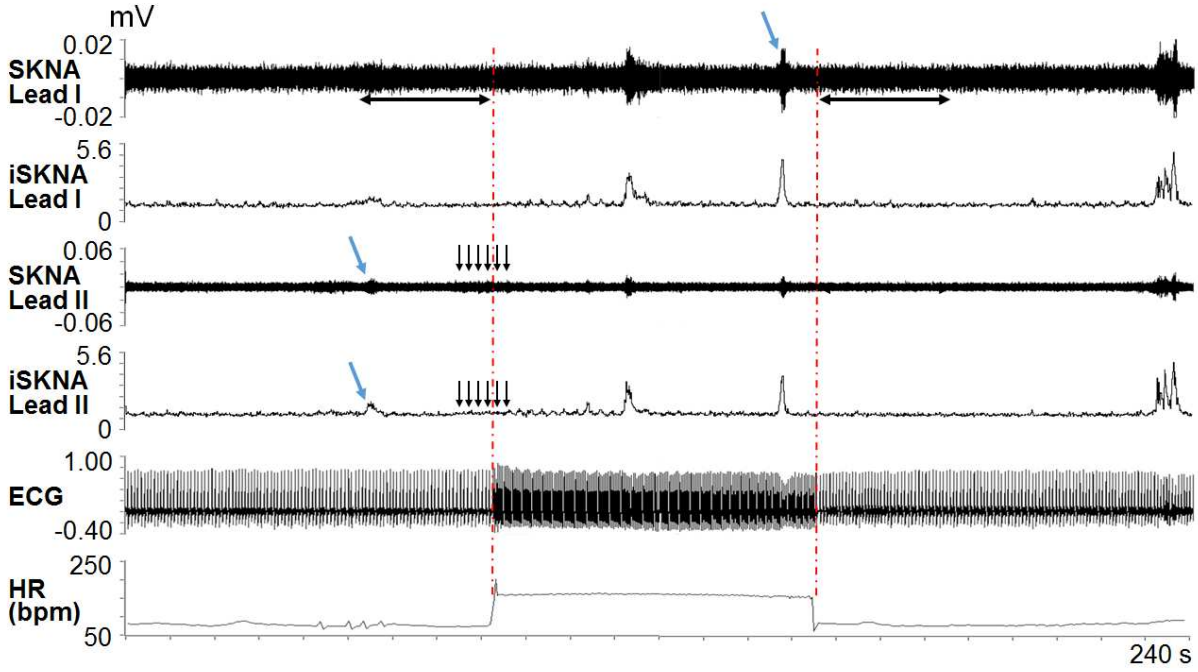

Figure 2. NeuECG recording of an AT episode from patient #1. SKNA is slightly elevated prior to (blue arrows) and at the onset of AT (downward black arrows). A short burst of SKNA (blue arrows) was observed prior to termination, but was not associated with HR acceleration. There was no SKNA elevation after termination. Each double headed arrow indicates 30 s.

ACCEPTED MANUSCRIPT

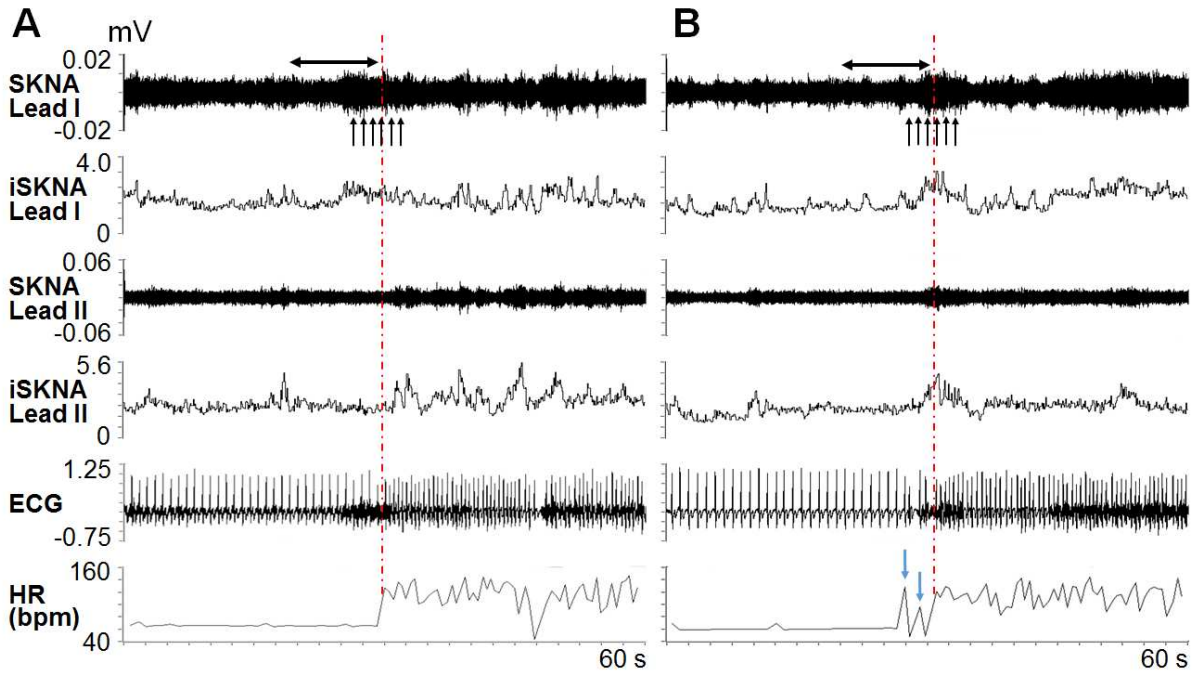

Figure 3. NeuECG recording of AF onset in patient #7. **(A)** SKNA is significantly increased prior to AF onset (black arrows). Double arrows indicate 10 s. **(B)** Similar findings in a separate AF episode of the same patient. SKNA is significantly increased prior to AF onset (black arrows). Two beats of premature atrial contractions preceded the onset (blue arrows), also associated with higher SKNA.

ACCEPTED MANUSCRIPT

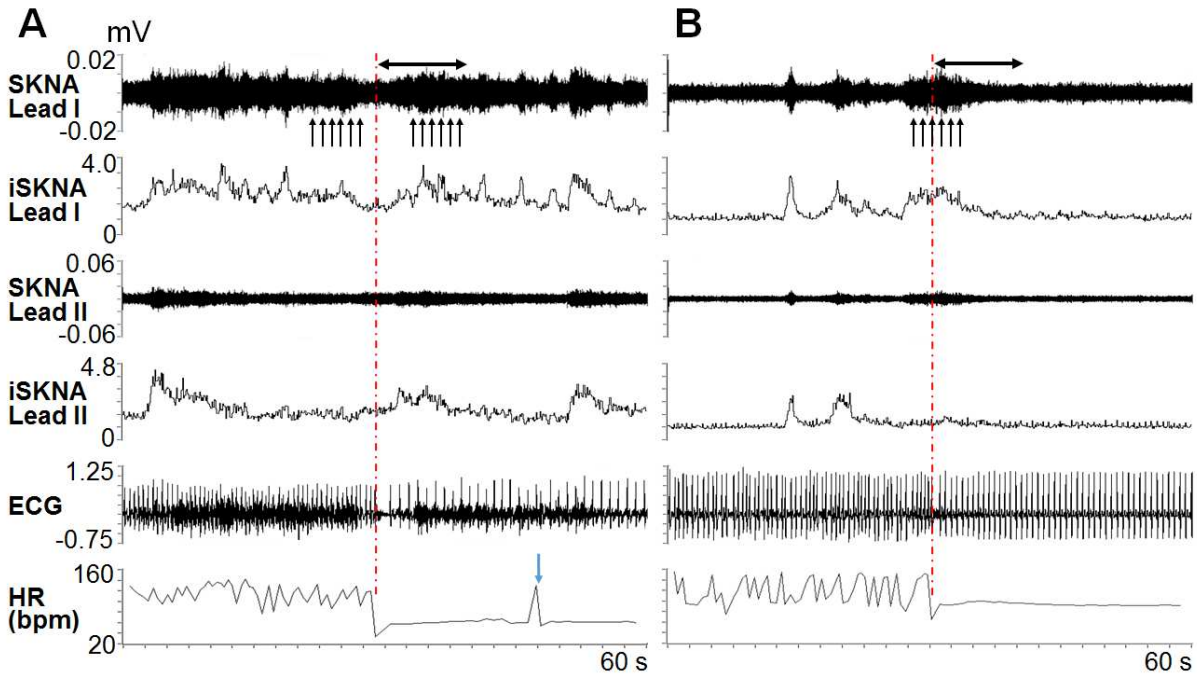

Figure 4. NeuECG recording of AF termination. **(A)** Significant increase in SKNA was observed in patient #7 before and after spontaneous termination of AF (black arrows). The double arrows indicate 10 s. A premature atrial contraction was recorded after termination of AF (blue arrow). **(B)** Similar to (A), increased SKNA was observed before and after termination of AF in patient #8.

ACCEPTED MANUSCRIPT

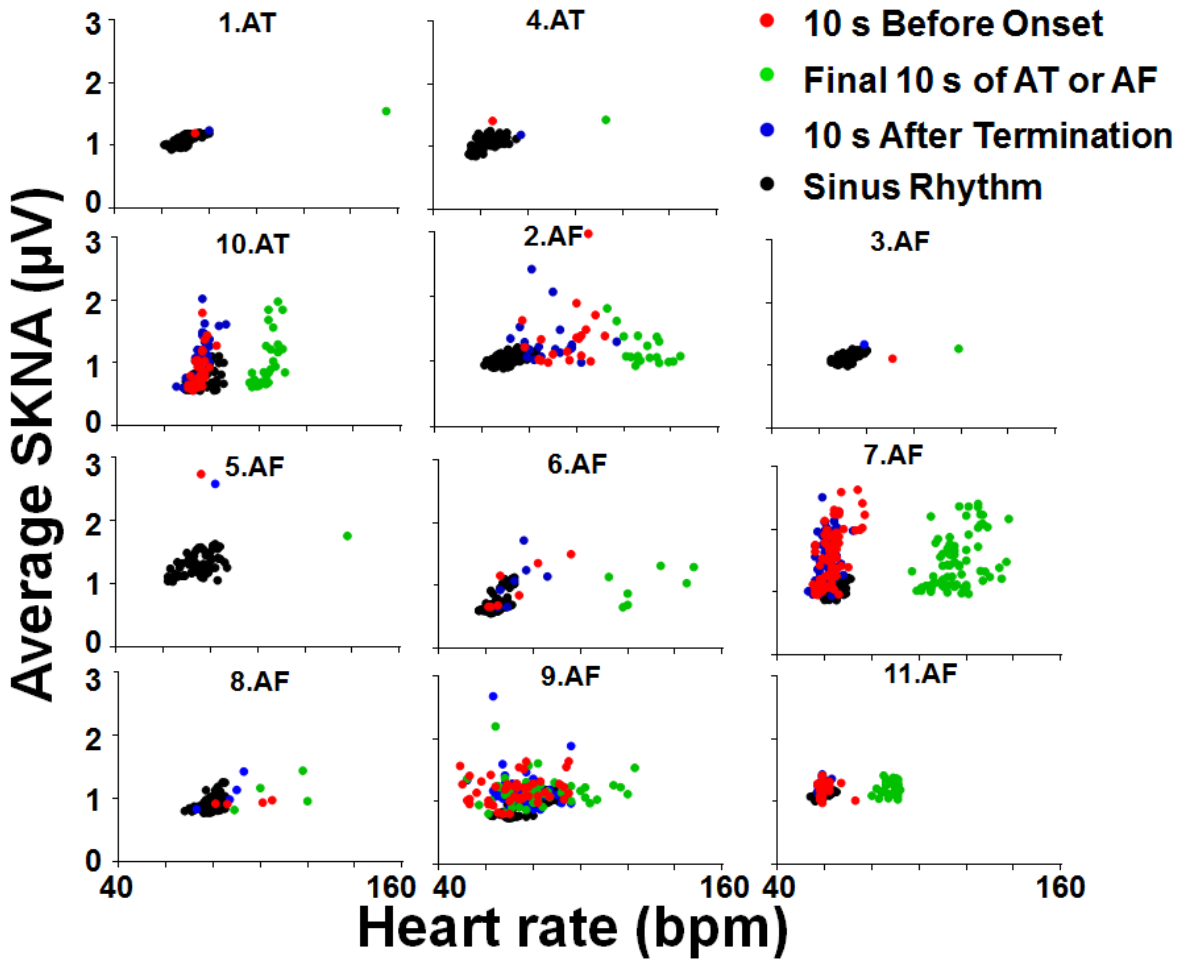

Figure 5. Characteristics of aSKNA and HR before, during last 10 s, and after AF or AT episodes. aSKNA before onset (red), during final 10 s (green) and after termination (blue) of both AT and PF episodes is greater than that of sinus rhythm (black) ($p<0.0001$). Overall, aSKNA before onset, during final 10 s and after termination of AF were both higher than that of AT. However, there is significant overlap within and variation among different individuals. For example, patient #10 had AT, but the aSKNA in this particular patient is higher than the other AT patients (#1, #4), as well as several AF patients (#3, #8, #11).

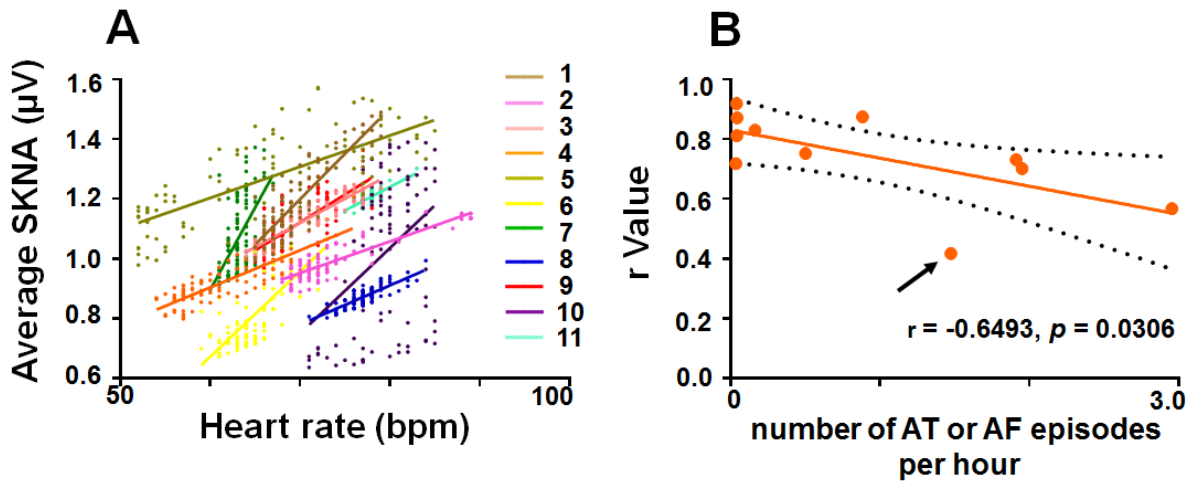

Figure 6. Correlation between aSKNA and HR and its relationship to frequency of AT or AF. **(A)** aSKNA and HR positively correlated with each other in all 11 patients. **(B)** Correlation coefficient of each patient is inversely correlated to the frequency of AT or AF episodes in the same patient. The more frequent a patient has AT or AF episodes, the less sensitive their HR is to sympathetic activation as detected by neuECG via skin. The outlier (black arrow) is from patient #10, who had > 100 short runs of AT but only 32 was ≥ 10 s and were included in the analyses. If we included all short burst of AT in the analyses, then his r value may not be lower than expected.