Patterns of baseline autonomic nerve activity and the development of pacing-induced sustained atrial fibrillation

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BACKGROUND Whether autonomic nerve activity is important in the development of pacing-induced sustained atrial fibrillation (AF) is unclear.

OBJECTIVE The purpose of this study was to test the hypothesis that patterns of baseline autonomic nerve activity are important in the development of pacing-induced sustained AF.

METHODS Radiotransmitters were implanted in 12 ambulatory dogs to record left stellate ganglion nerve activity (SGNA) and vagal nerve activity (VNA). Sustained (>48 hours) AF was induced with intermittent rapid atrial pacing.

RESULTS At baseline (before pacing), 1-minute integrated nerve activity between SGNA and VNA demonstrated either a single linear relationship with excellent correlation (group 1, N = 3, r = 0.816 ± 0.105) or nonlinear relationships with poor correlation (group 2, N = 9, r = 0.316 ± 0.162, $P < .05$ vs group 1). Group 1 dogs had higher VNA (97.0 ± 11.5 mV-s) compared to group 2 (33.4 ± 21.7 mV-s, $P < .001$). Group 1 dogs had more frequent sympathovagal co-activation episodes than did group 2 (50 ± 19 per day vs 15 ± 6 per day, $P < .05$) and more paroxysmal atrial tachycardia (PAT; 5 ± 1 per day vs 2 ± 1 per day, $P < .05$) at baseline. Sustained AF occurred after 16 ± 4 days (range 13–20 days) of pacing in group 1 and after 46 ± 18 days (range 23–72 days) of pacing in group 2 ($P < .05$). In the week before development of sustained AF, VNA of group 2 dogs was significantly increased compared to baseline ($P < .05$).

CONCLUSION Ambulatory dogs with good linear sympathovagal correlation and higher vagal tone at baseline have more PAT episodes at baseline and faster induction of sustained AF by rapid pacing. Rapid atrial pacing increased the VNA of the remaining dogs before induction of sustained AF.

KEYWORDS Arrhythmia; Atrial fibrillation; Atrial pacing; Autonomic nervous system; Nerve recording

ABBREVIATIONS **AF** = atrial fibrillation; **GP** = ganglionated plexi; **ICNA** = intrinsic cardiac nerve activity; **PAT** = atrial tachycardia; **SGNA** = stellate ganglion nerve activity; **SLGP** = superior left ganglionated plexi; **SLGPNA** = superior left ganglionated plexi nerve activity; **VNA** = vagal nerve activity

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Introduction

Atrial fibrillation (AF) can be either paroxysmal or sustained. In patients with paroxysmal AF at initial clinical evaluation, progression to more sustained forms is slow and/or unusual. Progression is estimated to be approximately 10% at 1 year and 25% to 30% at 5 years despite pharmacologic therapy.[1] In patients with lone AF, only about half progressed to sustained AF after 25-year follow-up.[2] Even if progression occurs, the transition rate varies considerably among individuals.[2] Reasons for such disparity in the susceptibility to AF progression remain poorly understood. It is known that intermittent rapid atrial pacing in large animals can lead to paroxysmal AF.[3,4] If rapid pacing continues, sustained AF will develop.[5] However, even with the same pacing protocol, sustained AF develops with variable durations of pacing among different animals.[3,5–7] The cause of such disparity of susceptibility to pacing-induced sustained AF is unclear. Wijffels et al[5] proposed that AF begets AF through progressive pacing-induced electrical remodeling, such as shortening of effective refractory periods. However, they also noted that the time course of changes in atrial refractoriness does not run completely parallel with the time course of development of sustained AF. These findings suggested to the authors that,

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besides the shortening of refractoriness, other factors may play a role in the development of chronic fibrillation. A possible factor is autonomic nerve activity, as radiofrequency catheter ablation of vagal innervation could abolish pacing-induced sustained AF.[8] However, no studies have compared the patterns of baseline nerve activity with the duration of rapid pacing needed to induce sustained AF. To determine if autonomic nerve activity is important in the development of sustained AF, we developed methods to perform long-term recording of nerve activity in ambulatory dogs and used rapid atrial pacing protocol to determine the duration of pacing needed to induce sustained (>48 hours) of AF. The results were used to test the hypotheses that (1) differential patterns of interactions among cardiac autonomic structures naturally exist at baseline (before pacing) and (2) certain distinct patterns of autonomic interactions are associated with quicker development of sustained AF.

Methods

The animal protocol was approved by the Institutional Animal Care and Use Committee of the Cedars-Sinai Medical Center,[3] Los Angeles, California, and Indiana University School of Medicine[4] and conforms to the guidelines of the American Heart Association.

Chronic ambulatory autonomic nerve recordings and pacing-induced AF

Twelve mongrel dogs of either sex (age >2 years, weight 22–27 kg) were studied over the past 5 years to determine the relationship between nerve activity and AF. The relationship between spontaneous paroxysmal AF and nerve activity in these dogs has been reported previously, including four dogs reported by Tan et al[3] and six dogs reported by Choi et al.[4] (The study by Tan et al[3] included a total of seven dogs without cryoablation. Three dogs studied more than 5 years ago were excluded because the data format used at that time was incompatible with the custom-written analyses software used in the present study). Two dogs not used in the previous reports were also included in this study. All 12 dogs underwent the same surgical procedures, including a left thoracotomy through the fourth intercostal space under isoflurane general anesthesia. Radiotransmitters (D70-EEE, Data Sciences International, St. Paul, MN, USA) were used in all 12 dogs to record left stellate ganglion nerve activity (SGNA) and vagal nerve activity (VNA). Intrinsic cardiac nerve activity (ICNA) was successfully recorded from the superior left ganglionated plexi (SLGP) in 8 of the 12 dogs. A pacing lead was implanted onto the left atrial appendage and connected to a Medtronic Itrel neurostimulator (N = 4)[3] or a modified Medtronic Kappa pacemaker (N = 8; Medtronic, Inc., Minneapolis, MN, USA) for intermittent high-rate atrial pacing.[4] All 12 dogs underwent the same pacing protocol, which included alternating 6-day pacing with 1-day monitoring until sustained (>48 hours) AF was documented. The dogs were then euthanized.

Data analysis

Data from each dog were studied to determine the actual number of days of pacing needed to induce sustained AF (net pacing days). Nonpaced days were excluded from this analysis. Recordings from all channels were manually analyzed. Nerve activity was considered present if a threefold increase in amplitude over baseline noise was observed. Co-activation was considered to be present when activation of two or more nerve structures overlapped for at least 5 seconds. In addition, the occurrence of paroxysmal atrial tachycardia (PAT) at baseline was determined. PAT was

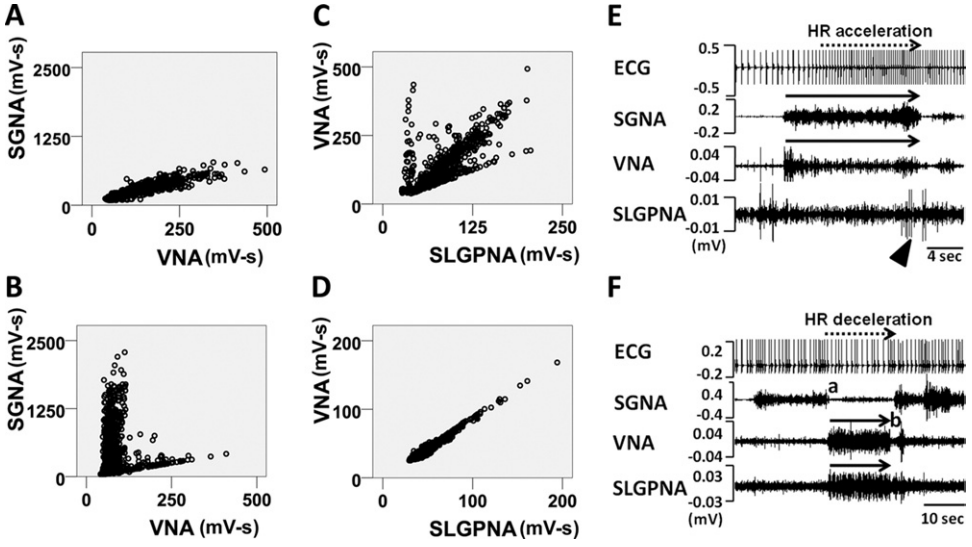

Figure 1 Patterns of autonomic interactions. **A:** Representative SGNA–VNA scatter plot of a group 1 dog. Each dot represents an SGNA–VNA pair of nerve activity integrated over 1 minute. The entire plot has 1,440 data points covering a 24-hour period. **B:** Representative SGNA–VNA scatter plot from a group 2 dog. **C:** Representative VNA–SLGPNA scatter plot from a group 1 dog. **D:** Representative VNA–SLGPNA scatter plot from a group 2 dog. **E:** Example of simultaneous sympathovagal co-activation *(black arrows)* observed in a group 1 dog that led to heart rate acceleration. *Arrowhead* indicates independent SLGPNA. **F:** Example of recording from a group 2 dog showing that simultaneously increased VNA and SLGPNA *(black arrows)* resulted in heart rate deceleration. ECG = electrocardiogram; SGNA = stellate ganglion nerve activity; SLGPNA = superior left ganglionated plexi nerve activity; VNA = vagal nerve activity.