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Recording Intrinsic Nerve Activity at the Sinoatrial Node in Normal Dogs with High-density Mapping

Running title: *Yang et al.; Nerve activity recorded from the SA Node*

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Abstract:

Background - It is known that autonomic nerve activity controls the sinus rate. However, the coupling between local nerve activity and electrical activation at the sinoatrial node (SAN) remains unclear. We hypothesized that we would be able to record nerve activity at the SAN to investigate if right stellate ganglion (RSG) activation can increase the local intrinsic nerve activity, accelerate sinus rate, and change the earliest activation sites (EASs).

Methods – High-density mapping of the epicardial surface of the right atrium (RA) including the SAN was performed in 6 dogs during stimulation of the RSG, and after RSG stellectomy. A radiotransmitter was implanted into 3 additional dogs to record RSG and local nerve activity at the SAN.

Results – Heart rate accelerated from 108±4 bpm at baseline to 125±7 bpm after RSG stimulation (P=0.001), and to 132±7 bpm after apamin injection (P<0.001). Both electrical RSG stimulation and apamin injection induced local nerve activity at the SAN with the average amplitudes of 3.60±0.72 μV and 3.86±0.56 μV, respectively. RSG stellectomy eliminated the local nerve activity and decreased the heart rate. In ambulatory dogs, local nerve activity at the SAN had a significantly higher average Pearson correlation to heart rate (0.72±0.02, P=0.001) than RSG nerve activity to HR (0.45±0.04 P=0.001).

Conclusions – Local intrinsic nerve activity can be recorded at the SAN. Short bursts of these local nerve activities are present before each atrial activation during heart rate acceleration induced by stimulation of the right stellate ganglion.

Key words: mapping; sinoatrial node; sympathetic nerve activity; stellete ganglion

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Nonstandard Abbreviations and Acronyms

aSGNA - average SGNA

ChAT - choline acetyltransferase

EAS - earliest activation site

GP - ganglionated plexi

PAT - paroxysmal atrial tachyarrhythmia

SAN - sinoatrial node

SGNA - stellate ganglion nerve activity

TH - tyrosine hydroxylase

Introduction

Nerve activity from both the intrinsic cardiac nervous system and the extrinsic cardiac nervous system has been shown to influence the heart rate.[1] For the extrinsic cardiac nervous system, recordings from the stellate ganglion have shown that stellate ganglion nerve activity (SGNA) often precedes heart rate (HR) acceleration and spontaneous cardiac arrhythmia in ambulatory dogs.[1] For the intrinsic cardiac nervous system, it has been shown that nerve activity from the anterior right ganglionated plexi (GP) within the fat pad of the sinoatrial node (SAN) has the greatest effect on SAN function.[2, 3] Histological studies showed that the nerve fibers extend out from this GP and into the actual pace-making area.[4] Several studies have been performed that

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have recorded the nerve activity from either the stellate ganglion, the GPs, or both, and these recordings have indicated a strong correlation to heart rate.[5-8] However, because of technical difficulties, no studies have simultaneously recorded both local SAN nerve activities and electrograms to determine the relationship between these two different electrical signals at the time of HR acceleration. Therefore, the importance of local SAN nerve activity on HR acceleration remains unclear. It is possible to selectively display the low frequency myocardial electrical activity and high frequency nerve activity from the same digitized electrical signals using differential filtering techniques.[8] We hypothesize that the same techniques can be used to simultaneously display both high frequency local nerve activity and low frequency atrial electrograms at the SAN. The purpose of the present study was to record from the epicardial surface of the SAN to test the hypotheses that (1) intrinsic cardiac nerve activity can be recorded within the SAN region and (2) local intrinsic cardiac nerve activity bursts drives HR acceleration.

Methods

The animal protocol was approved by the Institutional Animal Care and Use Committee of the Indiana University School of Medicine and the Methodist Research Institute, Indianapolis, IN, and conformed to the regulations for humane care and treatment of animals established by the NIH. The raw data that support the findings of this study are available from the corresponding author upon reasonable request. A total of 9 mongrel dogs of either sex (23-28 kg) with structurally normal hearts were studied within 2 different protocols as described in the Data

Supplement. Protocol 1 (n=6) consisted of high-density mapping of the SAN at baseline and then during the following conditions: (1) right stellate ganglion stimulation with a standard Grass Stimulator (Grass Technologies, Warwick, RI) with 20-Hz, 2-ms pulse duration, and 5-V output; (2) apamin (100 nmol/L, 1 ml) injected into the right stellate ganglion to activate the nerves; (3) right stellate ganglion stellectomy. Data was acquired during normal sinus rhythm and 10 min after the initiation of each intervention. All animals were euthanized at the end of the study and the right atrium was obtained in each dog for histological analysis. Protocol 2 (n=3) consisted of investigating the effects of spontaneous right stellate ganglion nerve activity on intrinsic cardiac nerve activity within the SAN region in ambulatory dogs. A radio-transmitter (D70EEE, Data Sciences International, St. Paul, MN) with 3 pairs of bipolar electrodes was implanted with a pair of bipolar electrodes sutured to the right stellate ganglion, a second pair was sutured over the sinoatrial node, and the third pair was sutured onto the right atrial ventral fat pad to record the local atrial activation. The DSI radio-transmitter was turned on and continuous recordings were started after the dogs were allowed to recover for 2 weeks. After a two-week recording period, the dogs were euthanized.

Statistical Analysis

All measurement data are expressed as mean ± SD. Values before and after each intervention during high-density mapping were compared using a paired *t* test. To compare the heart rate, a one-way analysis of variance was used to compare the heart rate among all interventions, and a paired *t* test was used to compare the heart rate between alpha-chloralose and the other interventions. A two-sided p- value ≤ 0.05 was considered statistically significant. A Pearson

correlation coefficient was used to compare the nerve activity recorded between the right stellate ganglion and the SAN, and to compare the nerve activity and heart rate. All statistical analyses were performed using SPSS software (version 18.0, SPSS, Inc, Armonk, NY).

Results

Protocol 1: High-density mapping of the Sinoatrial Node

The electrograms recorded from the plaque were manually reviewed for signal quality. Electrograms that contained mostly 60 Hz noise and/or far-field artifacts were eliminated from the analysis. An average of 702 signals were analyzed for each dog. Signals were manually reviewed and annotated for bursts of nerve activity. At baseline, after alpha chloralose was started in 6 dogs, the average amplitude of the right stellate ganglion nerve activity was 4.03±0.29 μV, which increased to 98.02±19.91μV after apamin injection (P<0.001). Figure 1 shows the average heart rate during a 12 second baseline recording during each intervention. As the figure shows, there was a significant acceleration of the heart rate with stimulation of the right stellate ganglion with both electrical pacing and apamin injection.

Intrinsic and Extrinsic Cardiac Nerve Activity

In each dog that was mapped, during right stellate ganglion stimulation (pacing and apamin injection), burst activity was observed prior to each atrial activation only in the SA nodal region. Nerve activity was not observed in any other locations within the mapped region of the right atrium. Figure 2 shows the locations of the electrodes where nerve activity was seen in the recorded electrograms. After a right stellate ganglion stellectomy, this burst activity was no

longer observed. Examples of the nerve activity are shown in Figure 3 with expanded recordings in Figure 4. The average amplitude of the intrinsic cardiac nerve activity between atrial activations was 3.60±0.72 μV with right stellate ganglion stimulation and 3.86±0.56 μV with apamin injection.

The movement of the earliest activation site

By using high-density mapping, we observed that the earliest activation site (EAS) changed with increased right stellate ganglion stimulation. The earliest activation sites of the SAN moved cranially by 5.1±2.2 mm when stimulating right stellate ganglion and by 5.2±1.0 mm after injecting apamin. After a stellectomy, the earliest activation sites of the SAN moved caudally, returning to a site similar to that of baseline. Figure 2B shows the locations of the earliest activation site for each intervention in each dog. Activation mapping in Figure 3 shows an example of this movement of the earliest activation site with right stellate ganglion stimulation.

Histological Examination

At the end of each experiment, the right atrial free wall including the SAN was preserved for Gap43, TH, and ChAT staining. Figure 2A shows the locations of the tissue samples used for analysis. As Figure 5 shows, more cells in and around the SAN displayed positive staining as compared to the cells in the right atrial free wall.

Protocol 2: Local nerve activity at sinoatrial node in normal ambulatory dogs

In order to determine if the intrinsic cardiac nerve activity at the SAN occurred spontaneously or if it is correlated with right stellate ganglion nerve activity, a DSI radiotransmitter was implanted with a bipolar electrode placed on the right stellate ganglion and another bipolar electrode placed

on the SAN. Overall, the average heart rate was 109±6 beats per minute (n=3), the average right stellate ganglion nerve activity was 2.69±0.15μV, and the average local nerve activity at the SAN was 3.26±0.43μV.

Similar to the observations made with the high-density plaque mapping, intrinsic cardiac nerve activity was observed within the SAN region in each of the ambulatory dogs. Figure 6 shows an example of the burst of nerve activity seen between each atrial activation. Also, this figure shows an example of the right stellate ganglion nerve activity occurring simultaneously with intrinsic cardiac nerve activity at the SAN (panel A), and an example of the intrinsic cardiac nerve activity at the SAN occurring before the right stellate ganglion nerve activity (panel B). Data Supplement Figure 1 shows the correlation between the SAN nerve activity and HR, right stellate ganglion nerve activity and HR, and SAN versus right stellate ganglion nerve activity for one dog over a 24-hour period. As the figure shows, there was a stronger correlation between the nerve activity at the SAN and HR (R=0.78, p=0.0001) as compared to right stellate ganglion nerve activity and HR (R=0.49, p=0.0001). The correlation coefficients for each individual dog are shown in table 1.

Episodes of PATs were observed in each of the ambulatory dogs with an average of 15±2 episodes over 24-hours per dog. Nerve activity was observed before the onset of each documented PAT. SAN nerve activity occurred before right stellate ganglion nerve activity in 27.6% of the episodes. Data Supplement Figure 2 shows an example of SAN nerve activity and right stellate ganglion nerve activity occurring simultaneously (Panel A) before PAT onset, and an example of SAN nerve activity occurring independently of right stellate ganglion nerve

activity before PAT onset (Panel B). Also observed was simultaneous right stellate ganglion nerve activity and SAN nerve activity prior to PAT termination. This phenomenon occurred in all of the observed PAT terminations.

Discussion

The high-density mapping protocol of this study demonstrated that 1) It is possible to simultaneously record local atrial electrogram and intrinsic cardiac nerve activity using high-density mapping techniques at the SAN; 2) increased right stellate ganglion activation had a direct effect on the local activation of nerve activity at the SAN; there was one burst of nerve activity before each atrial activation. This correlation disappeared after a right stellate ganglion stellectomy, providing support that the bursts prior to the local atrial electrograms were in fact nerve activities. Recordings from the ambulatory dogs demonstrated that (1) local nerve activity was increased with increased right stellate ganglion nerve activity; (2) intrinsic cardiac nerve activity at the SAN could occur independently of right stellate ganglion nerve activity; 3) local nerve activity at the SAN had a stronger correlation to HR than right stellate ganglion nerve activity. In each protocol, nerve activity within the SAN correlated to a change in heart rate. These results demonstrate that nerve activity can be recorded at the SAN region and that these recordings can provide new insights into the neural control of SAN function.

SAN dysfunction broadly describes a wide range of electrophysiological abnormalities, including persistent inappropriate sinus tachycardia, inappropriate sinus bradycardia, sinus arrest, SAN exit block, tachycardia-bradycardia (tachybrady) syndrome and chronotropic

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incompetence. It has also been shown that heart failure is associated with SAN dysfunction. Because the mechanism of SAN dysfunction and heart rate control are not completely understood, there are no mechanism-based therapies for SAN dysfunction. Understanding the mechanisms of SAN dysfunction may lead to the better prevention and treatment of this disorder. Furthermore, understanding the mechanisms of automaticity may improve the management of tachyarrhythmias, many of them are due to abnormally increased automaticity.

Local nerve activity at SAN

The SAN is innervated with both sympathetic and parasympathetic post ganglionic fibers from the intrinsic cardiac nervous system.[9] During sympathetic activation, it is expected that the neurotransmitters secreted from the sympathetic nerve terminals or adrenal glands will activate beta receptors to enhance automaticity. Because SAN is supplied by the SAN nodal artery, the elevated circulatory epinephrine and norepinephrine are sufficient to result in sustained SAN acceleration. However, the latter mechanisms of SAN rate acceleration may not be sufficient for the fight and flight response, which requires immediate activation of the SAN to accelerate the HR prior to the arrival of the catecholamines through the circulation. In the present study, we provided the first evidence that during right stellate ganglion activation, there is one burst of sympathetic nerve activity prior to each heartbeat which correlated to an increase in heart rate. This finding has not been reported before and is unique based on our experience in recording nerve activities in dogs and in humans. An alternative explanation of these mid-diastolic electrical activity is the activation of the SAN itself, with subsequent conduction into the nearby atrium. Previous optical mapping studies of the canine SAN region showed a conduction delay

between SAN activation and local atrial activation.[10, 11] In addition, a conduction delay between the SAN and the right atrium has also been shown with simultaneous endocardial and epicardial mapping indicating that the SAN is insulated from the surrounding atria.[12] However, the electrical activity recorded with high-density mapping, was only observed during stimulation of the right stellate ganglion. It is unlikely that these very low amplitude local electrograms originated from the SAN cells. Therefore, we propose that these burst activities are local intrinsic cardiac nerve activity which are needed to exert an instantaneous tight control of the SAN by the sympathetic nervous system to accelerate heart rate.

Extrinsic and intrinsic nerve activity

Several studies have been performed investigating the effects of either extrinsic cardiac nerve activity or intrinsic cardiac nerve activity has on SAN function.[4, 13] The extrinsic cardiac nervous system is composed of the stellate ganglion which is formed by fusion of the inferior cervical ganglion and the thoracic ganglion.[14] Recordings of right stellate ganglion nerve activity has been shown to correlate to heart rate.[6] The intrinsic cardiac nervous system is mainly composed of ganglionated plexi (GP) located on the heart. Intrinsic cardiac nerve activity from the right atrial GP situated anteriorly has been shown to play the leading role in regulating SAN function.[2, 3] In addition, it has also been shown that nerve activity from other GP within the right atrium and left atrium can effect SAN function.[4] While the intrinsic nerve structures (ganglionated plexi) are also known to be important in regulating heart rhythm,[15] intrinsic cardiac nerve structures have been shown to remodel within a canine heart failure model. Even though there is increased stellate ganglion nerve activity, ganglionated plexi nerve activity is

decreased and there is a reduced heart rate response to ganglionated plexi stimulation.[16] While these studies have investigated the effect of nerve activity on SAN function, previous studies have not recorded nerve activity directly from the SAN region and correlated extrinsic cardiac nerve activity and/or intrinsic cardiac nerve activity to SAN nerve activity. The present study has demonstrated that nerve activity can be recorded directly from the SAN with high density mapping at high sampling rates. This nerve activity was only seen from electrodes that were placed directly on the SAN and not from other mapped regions of the RA. Histological analysis confirmed these findings as nerve structures were observed within the SAN region, but not within any of the other mapped regions of the right atrium.

Nerve activity from the extrinsic cardiac nervous system has been shown to correlate with nerve activity recorded from the intrinsic cardiac nervous system.[5] Choi et al demonstrated that in ambulatory dogs, most of the nerve activity recorded from the ligament of Marshall correlated to either stellate ganglion nerve activity or vagal nerve activity, while all of the nerve activity recorded from the superior left GP correlated with nerve activity from the extrinsic cardiac nervous system.[5] The present study has also shown that extrinsic cardiac nerve activity correlates with intrinsic cardiac nerve activity including that right stellate ganglion nerve activity can directly influence SAN nerve activity and heart rate. However, recordings from ambulatory dogs showed that SAN nerve activity can occur independently of right stellate ganglion nerve activity and correlate with atrial activation. It has previously been shown that the intrinsic cardiac nerve activity can occur independently of the extrinsic cardiac nerve activity,[5] and the current study supports what has previously been demonstrated. Intrinsic cardiac

neurons receive both efferent and afferent inputs which ultimately effect cardiac dynamics. Afferent inputs from mechanosensory and chemosensory nerve endings within the cardiovascular system could provide the stimulus needed for the intrinsic cardiac nerves to fire independently of the extrinsic cardiac nervous system.[17]

While right stellate ganglion nerve activity was shown to influence SAN nerve activity and heart rate, it has also been shown that right stellate ganglion nerve activity can influence the location of the earliest activation site of the SAN. Sympathetic stimulation in general tends to induce a cranial shift in the location of the pacemaker within the SAN[18] through the acceleration of the calcium clock.[11] Joung et al[19] reported that the superior SAN serves as the earliest activation site during sympathetic stimulation in patients without AF and in most patients with AF without sympathetic bradycardia. Nakajima et al also demonstrated a shift in the pacemaker location with sympathetic stimulation.[20] The current study supported these findings as stimulation of the right stellate ganglion induced a cranial shift in the earliest activation site of the SAN.

Nerve Activity and Atrial Tachycardia

The autonomic nervous system is known to play a role in the initiation of atrial arrhythmias.[1] In demonstrating this mechanism of arrhythmia onset, several studies have been performed investigating the importance of intrinsic cardiac nerve activity and extrinsic cardiac nerve activity as a trigger for atrial arrhythmias. These studies also include neuromodulation investigations and clinical trials.[1, 21, 22] The results from a study that recorded both extrinsic cardiac nerve activity and intrinsic cardiac nerve activity by Choi et al showed that PATs were

preceded by either extrinsic cardiac nerve activity, intrinsic cardiac nerve activity or both simultaneously.[5] The present study supported these previous investigations as all episodes of PAT in the ambulatory dogs were either preceded by intrinsic cardiac nerve activity from the SAN region or right stellate ganglion nerve activity.

Study limitations

In this study, it was demonstrated that nerve activity within the SAN region could occur independently of right stellate ganglion nerve activity. However, the nerve activity within the SAN region could have been influenced by nerve activity that originated from other GP within the atria. It has been shown that through GP interconnections, nerve activity from other GP can influence SAN function.[4] Since recordings were not made from other right atrial GP, it is not known if there are instances where they activated first. Second, while the UnEmap system has the potential to simultaneously record 1700 channels at 10 kHz, the sampling rate and recording duration significantly affected the amount of time it takes to save each data file. In order to ensure that each data file contained enough information to adequately analyze any recorded nerve activity and that the computing time needed to save each data file did not have a negative impact on the protocol, a 4 kHz sampling rate and a file duration of 12 seconds were selected. With the current data, we didn't have the ability to determine the relative distance between the individual epicardial electrodes and the intracardiac nerve bundles or correlated the nerve density to the amplitude of the high-frequency activity observed in the recordings. Anesthesia with morphine and alpha-chloralose was used to reduce the effects of the anesthesia on the autonomic nervous system. However, although considerations were made to avoid anesthetics that affect

the nervous system during the anesthetized dog experiments, we cannot exclude that the anesthesia used might have affected the results.

Conclusion

Intrinsic cardiac nerve activity within the SAN region can be recorded with high density mapping and in ambulatory dogs. A mid-diastolic burst of nerve activity is present before each atrial activation during heart rate acceleration induced by stimulation of the right stellate ganglion. From these recordings, it can be shown that extrinsic cardiac nerve activity has a direct effect on intrinsic cardiac nerve activity, increasing neuronal control of SAN function and heart rate. However, intrinsic cardiac nerve activity can occur independently of right stellate ganglion nerve activity and has a greater correlation to heart rate. The finding that intrinsic cardiac nerve activity within the SAN region can occur independently provides a potential mechanism for arrhythmia onset.

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Disclosures: none.

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Table 1. Correlation Coefficients of Data from Ambulatory Dogs.

	SAN vs HR	**RSGNA vs HR**	**SAN vs RSGNA**
Dog 1	0.78（*P*=0.001）	0.49（*P*=0.001）	0.54（*P*=0.001）
Dog 2	0.72（*P*=0.001）	0.46（*P*=0.001）	0.57（*P*=0.001）
Dog 3	0.70（*P*=0.001）	0.41（*P*=0.001）	0.52（*P*=0.001）

Figure Legends:

Figure 1. Average heart rate during a 12 second recording at baseline of each recording period.

Alpha chl – Alpha chloralose; RSG Stim – electrical stimulation of the right stellate ganglion.

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Figure 2. Location of the electrodes where bursts of nerve activity were observed and the location of the earliest activation sites during each intervention. (A) Schematic showing the positioning of the electrode plaque on the right atrium, the location of the electrodes where nerve activity was observed, and the location of tissue samples taken for histology and immunohistochemical analysis (grey boxes). (B) Schematic showing the location of the earliest activation sites during each intervention for each dog.

Figure 3. Movement of the site of earliest activation with stimulation of the right stellate ganglion. Activation mapping and local nerve activity of right atrium and sinoatrial node (SAN). A: Baseline. B: Electrical stimulation of the right stellate ganglion. C: Apamin injection into the right stellate ganglion. D: Right stellate ganglion resection. The earliest activation site moves cranially with stimulation of the right stellate ganglion through either pacing (5V, 20 Hz) or with apamin injection. When a stellectomy is performed, the earliest activation site moves caudally to a location similar to baseline. Burst activity (arrows) within the SAN region were observed near the earliest site of activation during stellate ganglion stimulation (B) and with apamin injection (C) but not at baseline (A) or after right stellate ganglion resection (D). Panels E, F, G represent TH stains from tissue samples obtained from the correlated marked regions within the mapped area.

Figure 4. Local nerve activity within the SAN. Expanded views of the burst activity (red arrows) that was observed prior to each atrial activation. A 12-second recording after each intervention is

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shown from an electrode within the SAN region along with the corresponding right stellate ganglion (RSGNA) recording. A: Alpha chloralose at baseline. B: electrical stimulation of the right stellate ganglion. C: Apamin injection into the right stellate ganglion. D: right stellate ganglion stellectomy. With both electrical and pharmacological stimulation of the stellate ganglion, burst activity was observed within the SAN region that correlated to an increase in heart rate. ICNA – intracardiac nerve activity; RSGNA – right stellate ganglion nerve activity

Figure 5. Immunohistochemical staining of tissue from the RA free wall (top panels) and the SAN (bottom panels) was performed with antibodies against tyrosine hydroxylase (TH, middle panels), growth associated protein 43 (GAP 43, left panels), and Choline Acetyltransferase (ChAT, right panels) to investigate neuronal cell density within the mapped regions. Increased TH, ChAT and GAP43-positive nerves are more evident in the SAN region.

Figure 6. Local nerve activity at SAN. A: The local nerve activity at the SAN co-activates with the RSGNA. (A. 30 seconds duration, a. 5 seconds duration). B: The local nerve activity at SAN precedes the RSGNA (B. 30 seconds duration, b. 5 seconds duration). A = atrial activation. V = ventricular activation. RSGNA – right stellate ganglion nerve activity; SAN - sinoatrial node

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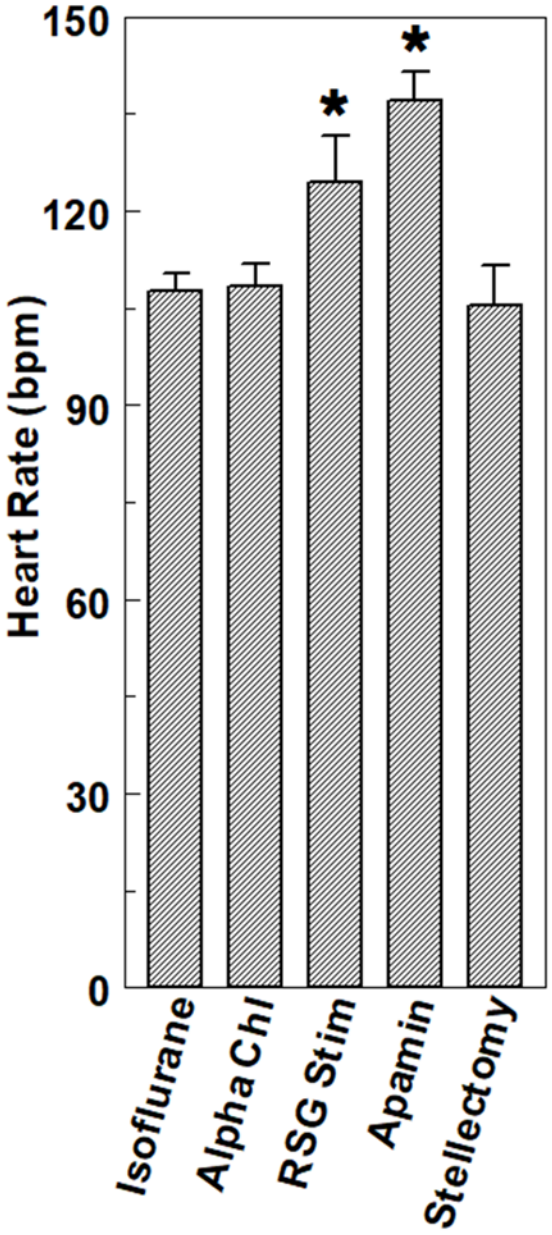
What Is Known?

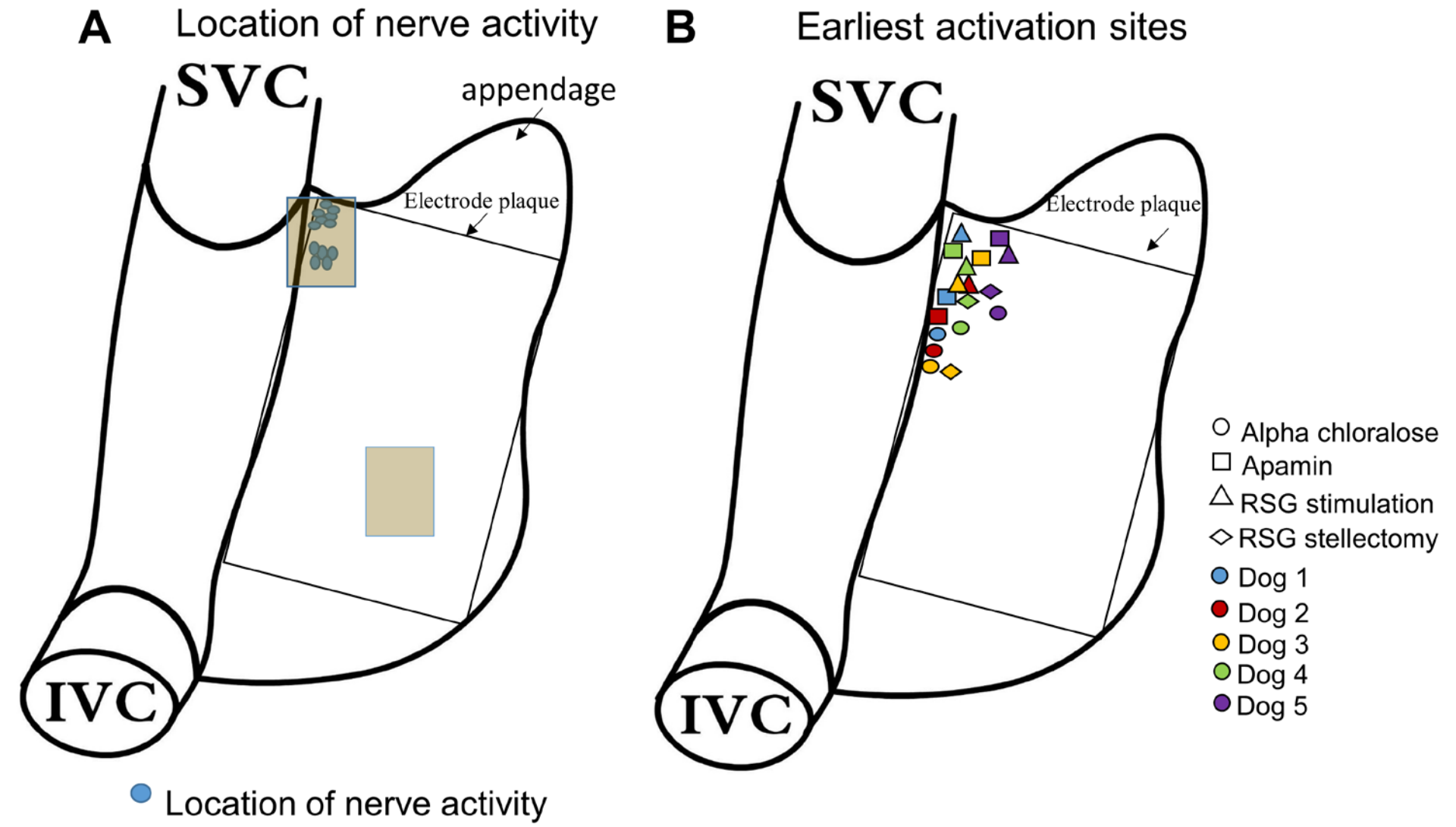
- Nerve activity from both the intrinsic cardiac nervous system and the extrinsic cardiac nervous system has been shown to influence the heart rate.
- For the extrinsic cardiac nervous system, recordings from the stellate ganglion have shown that stellate ganglion nerve activity often precedes heart rate acceleration and spontaneous cardiac arrhythmia in ambulatory dogs.
- For the intrinsic cardiac nervous system, it has been shown that nerve activity from the anterior right ganglionated plexi within the fat pad of the sinoatrial node has the greatest effect on sinus node function.

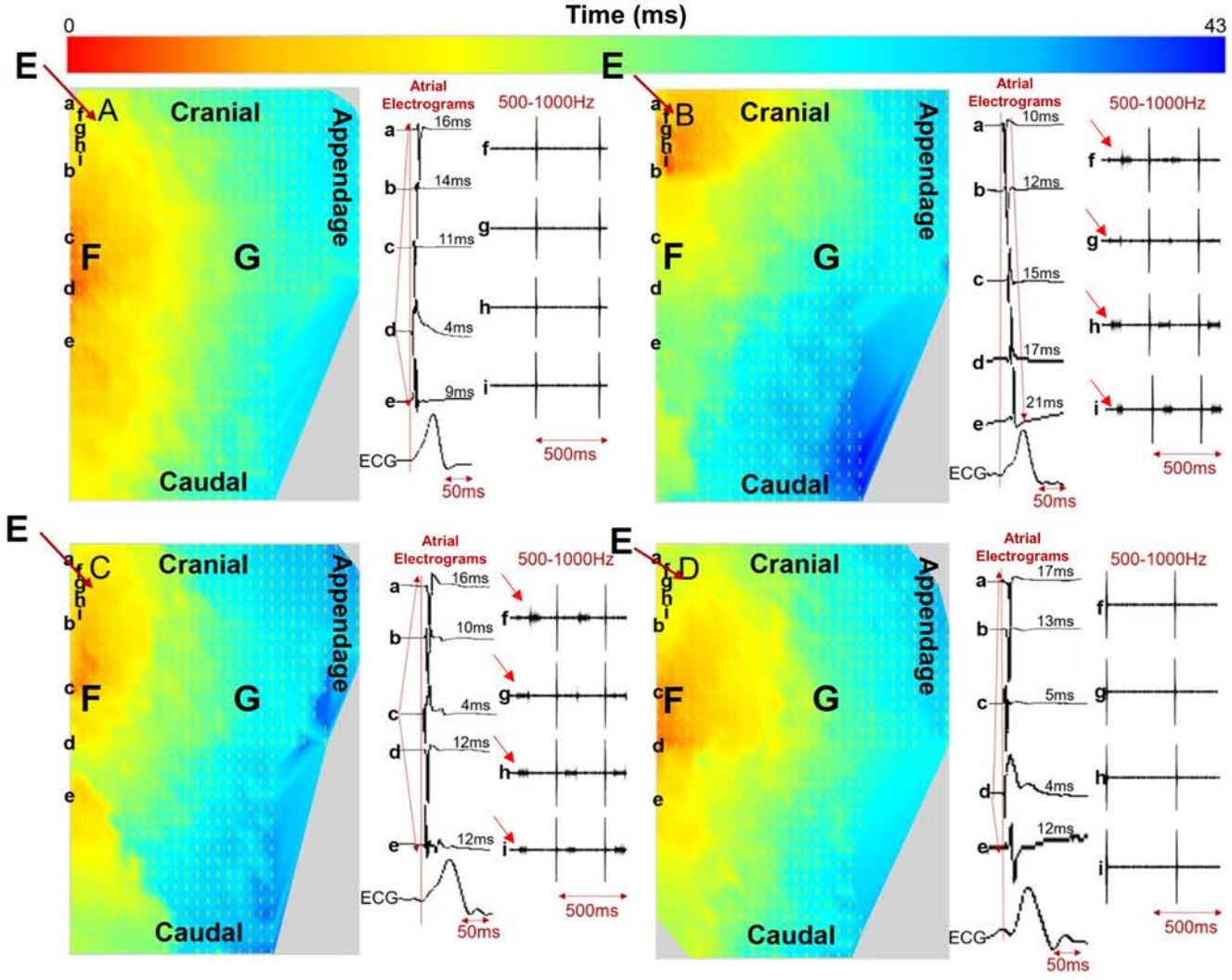
What the Study Adds?

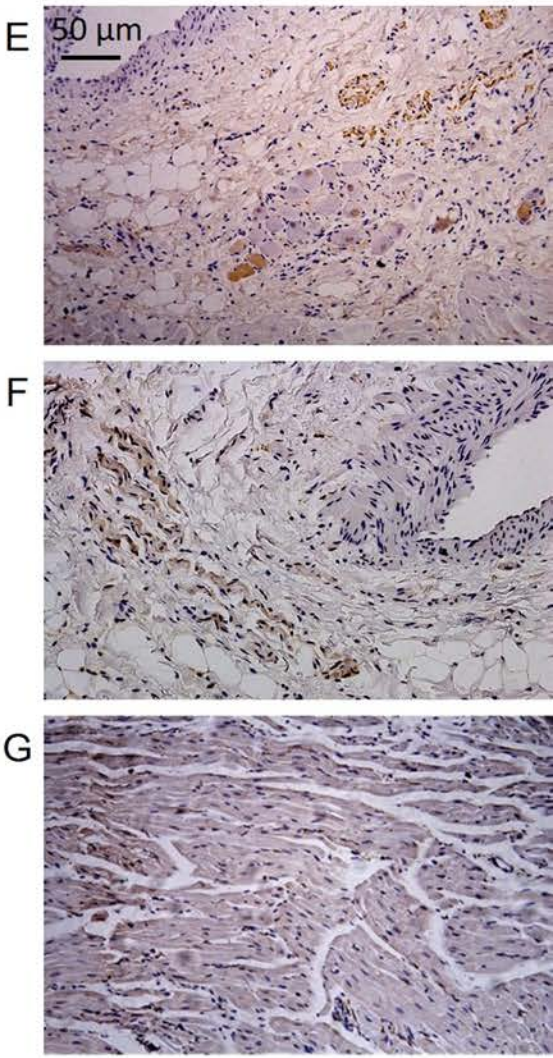
- Intrinsic cardiac nerve activity within the sinoatrial node region can be recorded with high density mapping and in ambulatory dogs.
- A mid-diastolic burst of nerve activity is present before each atrial activation during heart rate acceleration induced by stimulation of the right stellate ganglion.
- From these recordings, it can be shown that extrinsic cardiac nerve activity has a direct effect on intrinsic cardiac nerve activity, increasing neuronal control of sinoatrial node function and heart rate.

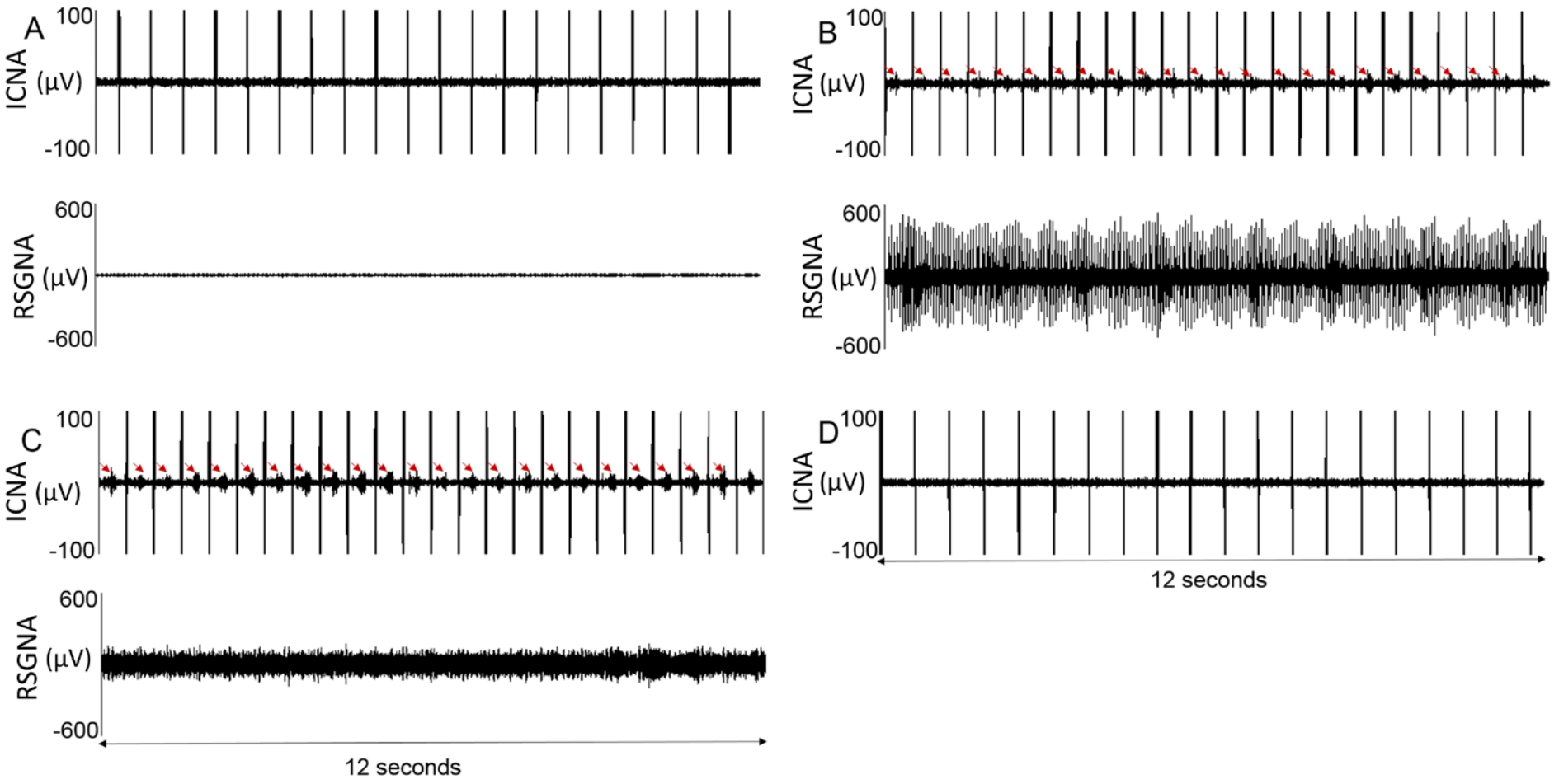


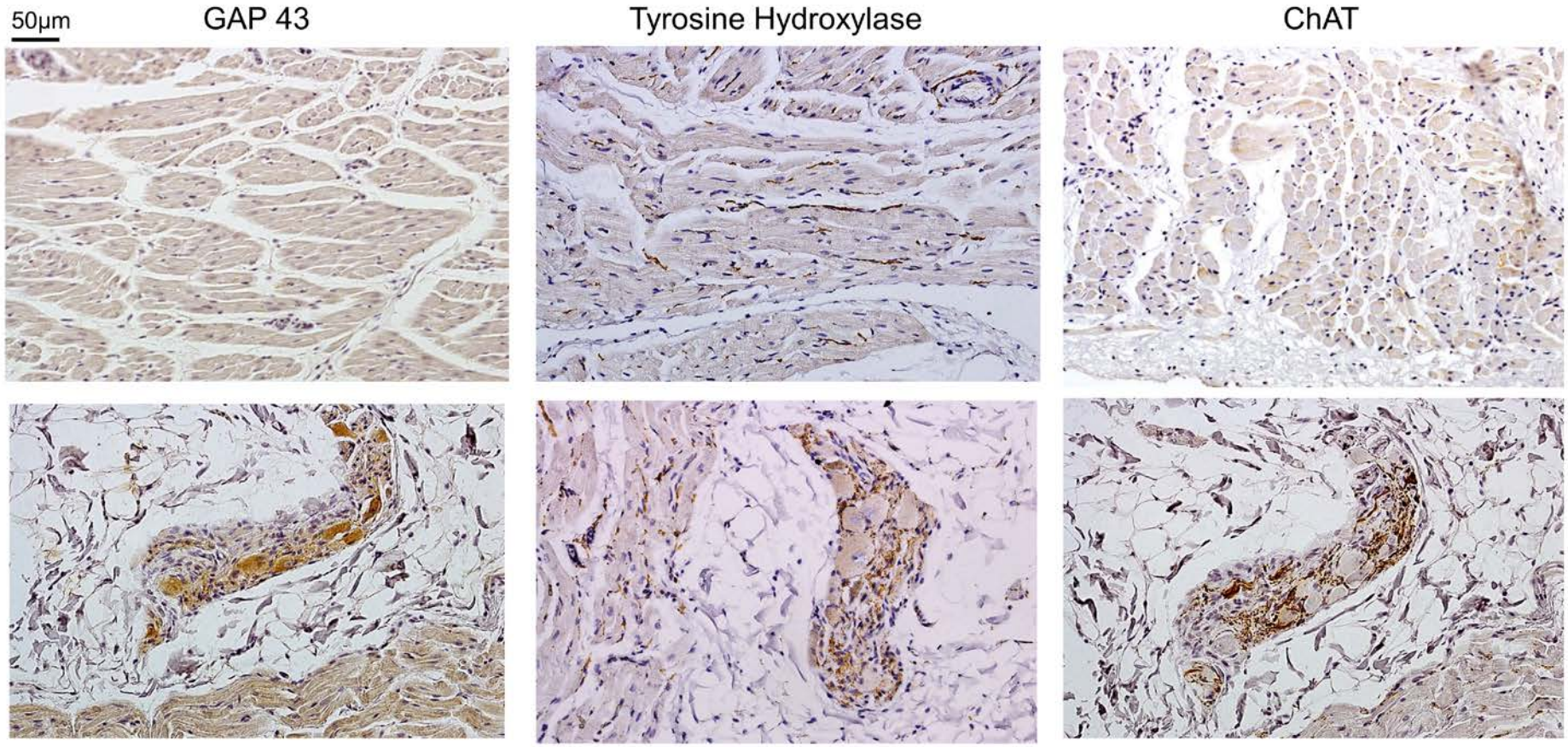
* p<0.01 vs alpha chloralose

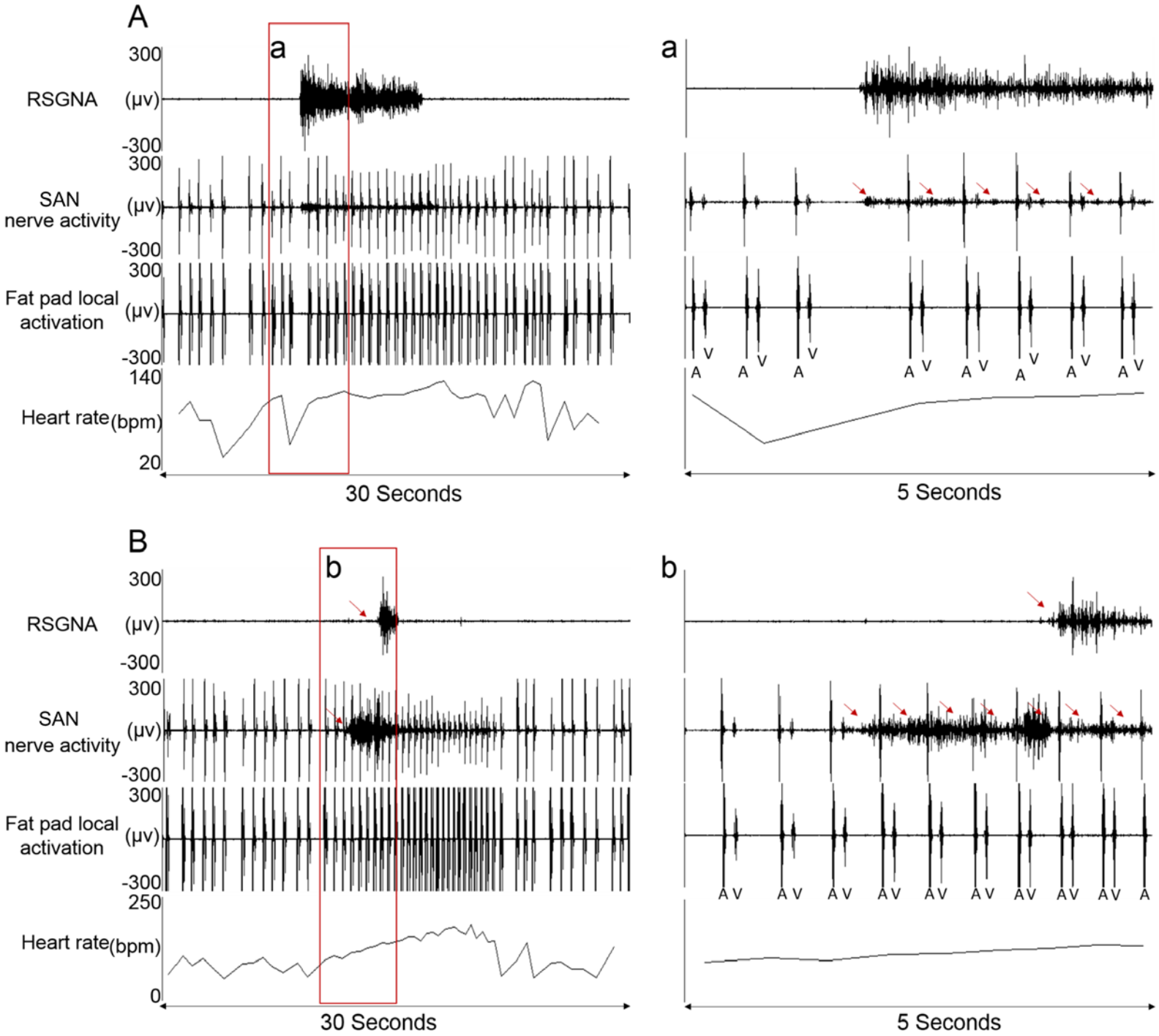

A
Location of nerve activity
SVC
appendage
Electrode plaque
IVC
Location of nerve activity
B
Earliest activation sites
SVC
Electrode plaque
IVC
Alpha chloralose
Apamin
RSG stimulation
RSG stellectomy
Dog 1
Dog 2
Dog 3
Dog 4
Dog 5


Time (ms)
0
43
E
A
Cranial
Appendage
Caudal
F
G
Atrial Electrograms
500-1000Hz
16ms
14ms
11ms
4ms
9ms
ECG
50ms
500ms
B
10ms
12ms
15ms
17ms
21ms
C
16ms
10ms
4ms
12ms
12ms
D
17ms
13ms
5ms
4ms
12ms


E
50 µm
F
G


A
ICNA
100
(μV)
-100
RSGNA
600
(μV)
-600
B
ICNA
100
(μV)
-100
RSGNA
600
(μV)
-600
C
ICNA
100
(μV)
-100
RSGNA
600
(μV)
-600
12 seconds
D
ICNA
100
(μV)
-100
12 seconds


50µm
GAP 43
Tyrosine Hydroxylase
ChAT
Right Atrium Free Wall
Sinoatrial Node


A
a
300
RSGNA
(μv)
-300
300
SAN
nerve activity
(μv)
-300
300
Fat pad local
activation
(μv)
-300
140
Heart rate
(bpm)
20
30 Seconds
a
A V A V A V A V A V A V A V A V
5 Seconds
B
b
300
RSGNA
(μv)
-300
300
SAN
nerve activity
(μv)
-300
300
Fat pad local
activation
(μv)
-300
250
Heart rate
(bpm)
0
30 Seconds
b
A V A V A V A V A V A V A V A V A
5 Seconds

Graphic Abstract

Intrinsic nerve activity at the sinoatrial node in normal dogs

Anesthetic dogs

Stimulate right stellate ganglion

The earliest activation site of SA node moves cranially

Recording intrinsic nerve activity within SA node region

Right stellate ganglion stellectomy

The earliest activation site of SA node moves caudally

Recording no intrinsic nerve activity within SA node region

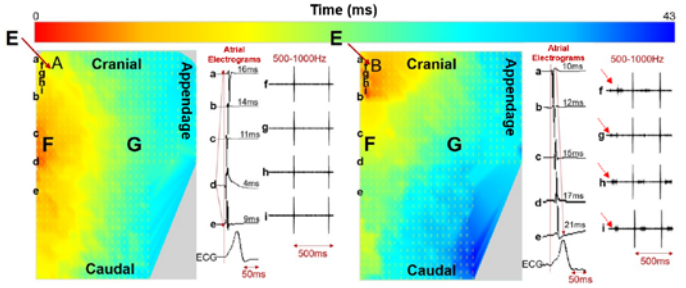
Ambulatory dogs

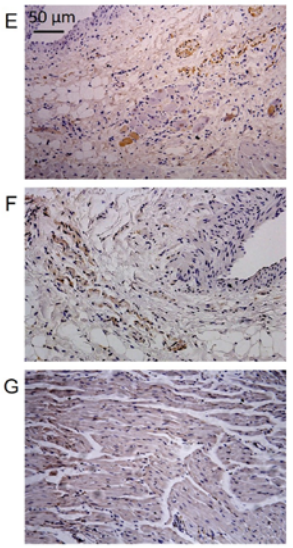
Recording right stellate ganglion nerve activity

Lower correlation with heart rate

Recording intrinsic nerve activity of SA node

Higher correlation with heart rate





Local intrinsic nerve activity can be recorded at the SA node. Short burst of these local nerve activities are present before each activation during heart rate acceleration induced by stimulation of the right stellate ganglion (B).