Lidocaine Converts Acute Vagally Associated Atrial Fibrillation to Sinus Rhythm in German Shepherd Dogs with Inherited Arrhythmias


Background: Lidocaine is most frequently used to treat ventricular arrhythmias. However, lidocaine may have an antiarrhythmic effect for certain supraventricular arrhythmias.

Hypothesis: We hypothesized that lidocaine would be effective in converting experimentally induced atrial fibrillation (AF) to sinus rhythm and that a decrease in the dominant frequency (DF) and an increase in the organization as judged by the spectral entropy (SE) would occur over the course of the conversion.

Animals: Seven German Shepherd (GS) Dogs.

Methods: Dogs were anesthetized with fentanyl and pentobarbital. AF was induced with standard pacing protocols while left and right atrial monophasic action potentials (MAP) were recorded. The power spectra from the MAP recordings were analyzed to determine DF and SE during treatment with boluses of 2 mg/kg lidocaine.

Results: Lidocaine converted AF to sinus rhythm in all dogs and all episodes (n = 19). Conversion time was 27–87 seconds. After atropine, sustained AF was not induced; however, 5 episodes of atrial tachycardia resulted, and 3 were converted with lidocaine. Frequency domain analysis of 12 conversion sequences showed that left and right DF of the MAP signals decreased from the time of injection to conversion to sinus rhythm (P < .001). Mean SE indicated a gradient between the left and right atria (P = .003) that did not change during conversion.

Conclusions and Clinical Importance: Vagally associated AF in GS dogs is terminated with lidocaine. Lidocaine is likely an effective treatment in clinical dogs with vagally associated AF.

Key words: Dominant frequency; Fentanyl; Spectral entropy; Vagal.

German Shepherd (GS) Dogs affected with inherited ventricular arrhythmias have an increased propensity to die suddenly when ventricular tachycardia degenerates into ventricular fibrillation.1,2 Although antiarrhythmic treatment administered PO has not been shown to suppress the arrhythmia adequately, IV lidocaine, a sodium (Na)-channel blocker, will convert the arrhythmia to sinus rhythm. We have noted that affected GS dogs will develop atrial fibrillation (AF) with certain perturbations (triggers) such as phenylephrine provoked baroreceptor reflex, passage of catheters through the right atrium, touching the atria during surgery, or pacing the right atrium.3 Serendipitously, we noted that, when we used lidocaine to treat dangerous ventricular tachycardia, the AF would convert to sinus rhythm.

Only 1 other study in the dog has reported successful pharmacologic cardioversion of vagally mediated AF with lidocaine.4 In that study, AF was induced with pacing under the conditions of increased parasympathetic tone achieved with either z-chloralose anesthesia or pentobarbital anesthesia with direct external electrical vagal stimulation.5 Recently, reports have been published with regard to the conversion of atrial tachycardia (AT) in dogs treated with lidocaine.6 Situations likely exist whereby AF is triggered in dogs in clinical circumstances that increase vagal tone. Treatment with lidocaine potentially could convert the AF to sinus rhythm and this outcome has been reported.5

The complexity of atrial electrograms or action potential recordings during AF has been a barrier to the understanding of the pathophysiology of AF. Recently, application of spectral techniques and frequency domain analysis to these signals has provided new insights into the mechanisms of AF and the responses to antiarrhythmic drugs.6 We have applied these new techniques in a companion study that examined the inducibility of AF in GS dogs under anesthesia protocols that increased vagal tone. The purpose of the companion paper was to determine whether premature stimuli alone would induce AF in these dogs and to assess whether this was true after treatment with atropine. We also sought to determine whether measures of the organization of the AF activity such as spectral entropy (SE) and dominant frequency (DF) were different between the left and right atrium. The study reported here concerns the cardioversion of induced AF to sinus rhythm by the Na-channel blocker lidocaine and the effects on SE and DF on the time of conversion.

In the present study, we hypothesized that lidocaine would be effective in converting vagally associated AF. We also hypothesized that frequency domain analysis of the atrial signal recorded from monophasic action potential (MAP) catheters during AF would provide useful information on the electrophysiologic alterations after lidocaine injection.
### Materials and Methods

All procedures were approved by the Cornell University Institutional Animal Care and Use Committee to ensure humane treatment of all dogs and legitimacy of the research. Moreover, dogs euthanized for this current study also had tissues collected for other investigations to maximize animal use.

#### Experimental Preparation

Seven GS dogs from a breeding colony with inherited ventricular arrhythmias and sudden death, weighing 25.7 ± 4.3 kg and 180 ± 20 days old were studied. Each of these dogs was determined to be afflicted with inherited ventricular arrhythmias on the basis of a minimum of three 24-hour ambulatory electrocardiographic recordings (Holter monitoring). Additionally, the presence of atrial arrhythmias was ascertained. Dogs were instrumented for 2 electrophysiologic protocols (extrastimulus and pacedown) for the induction of AF. Anesthesia was induced with fentanyl citrate at 0.02 mg/kg and pentobarbital at 10 mg/kg given as 2 sequential IV boluses. The dogs were intubated and ventilated with oxygen. Dogs were maintained under general anesthesia with a constant fentanyl infusion at a rate of 0.04 mg/kg/h through a cephalic IV catheter. Additional boluses of pentobarbital also were given as needed through a 2nd cephalic IV catheter to maintain adequate anesthesia. An infusion of lactated Ringer’s solution at 10 mL/kg/h was continued throughout the procedure. A catheter was placed in the pedal artery for recording peripheral blood pressure. One surface electrocardiographic lead in the frontal plan was recorded. All the recordings obtained during the experimentation were digitized using a data acquisition system. A left-sided thoracotomy through the 5th intercostal space and a pericardectomy were performed to expose both atria. Five bipolar electrodes were imbedded and sutured in place within the atrial wall. The 3 left-sided electrodes were placed in the region of the left appendage, the pulmonary vein left atrial junction and the left Bachman’s bundle, respectively. The 2 right-sided electrodes were placed in the region of the right atrial body and the right appendage, respectively. These electrodes were used for pacing and atrial electrogram recording. Two MAP catheters were held in place by an operator on the left and the right appendages for epicardial MAP recordings. The electrophysiologic protocols were performed from each of the 5 atrial electrodes with a stimulator using square impulses of 2 ms pulse duration at twice the stimulation threshold.

#### Extrastimulus Protocol for Induction of AF

We have shown that sustained AF in GS dogs can be induced with extrastimuli (premature) complexes that impinge on the effective refractory period (ERP). We delivered 1 or 2 premature stimuli to induce AF in the 7 dogs at each of the 5 atrial sites impaled with the electrodes. Stimuli were delivered at 2 basic cycle durations of 500 and 350 ms. Each site was paced with a pulse train of 20 stimuli (S1) followed by an extrastimulus (S2) with the coupling interval decreased in 20-ms steps between 200 and 160 ms, and in 10-ms steps from 150 ms to loss of capture. Pacing was then resumed by adding 10 ms to the S1–S2 interval that resulted in loss of capture and the S1–S2 interval again was decreased in 1-ms steps until loss of capture. A similar protocol was repeated with a train of 20 S1 stimuli followed by 2 premature S2–S3 stimuli.

#### Pacedown Protocol for Induction of AF

A dynamic pacedown protocol was then performed. Each atrial site was paced with 10 S1 stimuli with no pause between the pacing bursts starting at a pacing rate of 300 ms and decreasing the S1–S1 interval in 20-ms steps until 160 ms and then decreasing by 10-ms steps. Pacing was stopped when a 2:1 stimulus to atrial conduction block developed or when AF was initiated.

#### Protocol After Vagolytic

Atropine at 0.04 mg/kg was administered IV. The pacing protocols were repeated no sooner than 5 minutes after the atropine at 1 left or 1 right atrial site at which AF was induced, or if AF had not been induced, then from the pulmonary vein and atrial site or the body of the right atrium.

#### Defining AF and AT

AF was defined as the presence of “f waves” on the surface ECG with accompanying fragmented or multipotential electrograms with changing amplitudes and morphologies from at least 1 of the MAP recordings. Each episode of AF was reviewed to determine whether the induction was the result of a premature extrastimulus that occurred spontaneously, an extrastimulus from the pacing stimulus or from the pacedown pacing. AT was defined by the presence of distinct P waves on the surface ECG with a PP interval of <350 ms and MAP recordings that had distinctive nonfractionated electrograms. Moreover, AT was characterized by an abrupt change in atrial rate above the sinus rate.

#### Lidocaine Administration During AF and AT

When an episode of sustained AF or AT (defined as ≥8 minutes in duration) occurred, lidocaine at 2 mg/kg was given IV. To avoid excessive prolongation of the experiment, lidocaine was administered after 5 minutes of AF if at least one 8-min episode of AF requiring lidocaine conversion was documented. If conversion did not occur with the 1st injection, a 2nd bolus at the same dose was given.

#### Signal Analysis

The complexity of AF recordings, such as varying amplitude and morphology, makes manual analysis difficult. Frequency domain analysis of the signal helped overcome this limitation. Data were prepared by subtracting the 4-second moving average. A Hanning window was then applied to consecutive 4-second segments of the data, with no overlap between segments. A fast Fourier transform was then used to calculate power spectra for each of these segments of both left and right MAP recordings of sustained episodes of AF. The DC (0 Hz) component was then removed. The power spectra were then analyzed to determine DF and SE of the signal during conversion from AF to sinus rhythm. DF was defined for each time segment as the frequency containing the most power. It was used as an estimation of the atrial activation rate. SE is an index that indicates how widely power is distributed among various frequencies, and therefore is a measure of the randomness of the signal. Thus, low SE describes a more organized system and high SE corresponds to a less organized system. The fraction p of the total power at each frequency f was obtained by dividing each power spectrum component in a given time segment by the sum of all the power components in that segment. The SE for a given 4-second time segment was then calculated from

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SE = \frac{1}{M} \sum_{f=1}^{f_{max}} p(f) \ln p(f)
\]

The sum is over all recorded nonzero frequencies equal to or below the predefined frequency f_{max}, here chosen to be 14 Hz. This frequency was chosen because it was substantially > 10 Hz, which is the highest frequency of activation typically observed, and substantially lower than its 1st harmonic at 20 Hz, which contains
redundant information. The lowest nonzero frequency \( f_1 \) was 0.25 Hz, with 0.25 Hz separations between all recorded frequencies.

### Statistical Analysis

In order to facilitate statistical analysis of the frequency data, time was normalized for all DF and SE versus time records. Zero corresponded to the time of lidocaine injection, and 1 to the time of conversion. A commercial software program was used to interpolate SE data linearly in 20 divisions of normalized time duration 0.05 each over the length of time of the conversion in order to compare the SE over the period from injection to conversion. Analogous interpolation of the DF was not attempted, because it would have been inaccurate due to the large instantaneous variations often displayed by the DF data. These variations typically were caused by the frequent appearance of large-amplitude electrical alternans, which often would abruptly change the DF back and forth between its usual value and half that value. Therefore, for each episode, an equal number of DF data points starting at the time of lidocaine injection and including \( \approx 75\% \) of conversion time was selected for statistical analysis. All data sets were analyzed with the method of analysis of variance with repeated measures by the commercial statistical software.\(^k\) There were 2 repeated measure factors: side (LA versus RA) and time of a given response. The variability among dogs was treated as a between-subject (grouping) factor in the analysis of variance. For main effects, a value of \( P < .05 \) was considered significant, whereas for interactions, a value of \( .01 \) was considered significant. When a significant time effect was found, it was followed by orthogonal polynomial contrasts. Assessment of a violation of the sphericity assumption was made on the basis of the size of the Huynh-Feldt estimate of Epsilon. The tests were adjusted for the lack of sphericity by adjusting the degrees of freedom using the appropriate Huynh-Feldt estimate of Epsilon.

### Results

Six of 7 dogs developed sustained AF. Commonly, throughout the recordings, dogs would have ventricular tachycardia and AF (Fig 1). Lidocaine was given to the 6 dogs that developed sustained AF and to 3 dogs that developed sustained AT. All dogs that developed AT had been pretreated with atropine.

#### Conversion of AF with Lidocaine

A total of 19 episodes of sustained AF in 6 dogs were treated with lidocaine and all converted to sinus rhythm (Fig 2). In 16 episodes, a single bolus (2 mg/kg) of lidocaine converted the AF. Three episodes in 2 dogs required a 2nd injection. The time to conversion was brief (median, 58 seconds; range, 27–87 seconds). Visually, from the time of lidocaine administration, changes in the ECG and MAP recordings could be seen. The “f waves” of AF became more prominent and less fractionated as did the MAP recordings. Frequently, flutter waves or AT preceded conversion to sinus rhythm. The atrial rate during AF is approximately 500 bpm, and thus a decrease in this rate would be expected during conversion. However, it is very difficult to count this rate in patients and the spectral analysis documented the decreased frequency. Alternans was identified for varying durations of time during AF in all dogs on the left (Lt) MAP and right (Rt) MAP recordings and was characterized by a beat-to-beat fluctuation of the amplitude and the duration of the MAP.

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*Fig 1.* Electrocardiogram from German Shepherd Dog with atrial fibrillation (f waves present) and ventricular tachycardia (VT). Paper speed 25 mm/s. Bar indicates 1 second.

*Fig 2.* ECG and electrophysiologic recordings from a German Shepherd Dog with atrial fibrillation (AF). The conversion of AF to sinus rhythm is shown after treatment with lidocaine (2 mg/kg IV). Electrogram is from Bachmann’s Bundle (Bach Bundle), and epicardial monophasic action potential recordings are from the left (Lt MAP) and right (Rt MAP) auricles. The electrogram, Lt MAP, and Rt MAP recordings demonstrate the fractionated morphology characteristic of AF, which corresponds to the fibrillating waves on the surface ECG. Just before conversion to sinus rhythm, the electrograms become distinct unfractionated waveforms. Note the Rt MAP begins before that recorded on the left during sinus rhythm indicating origin in the sinus node from the right atrium. Bar lower right indicates 1 second.
A total of 5 episodes of AT in 3 dogs were treated with lidocaine and 3 of these episodes in 2 dogs converted from AT to sinus rhythm. Conversion in each dog occurred in $<90$ seconds (Fig 3).

**Conversion of AT with Lidocaine**

A total of 5 episodes of AT in 3 dogs were treated with lidocaine and 3 of these episodes in 2 dogs converted from AT to sinus rhythm. Conversion in each dog occurred in $<90$ seconds (Fig 3).

**Dominant Frequency and Spectral Entropy after Lidocaine Injection**

The DF and SE analysis of the Lt MAP and Rt MAP signals permitted an investigation of the alterations of the atrial electrical activity from the time of lidocaine injection to AF conversion to sinus rhythm. Adequate signals were available from a total of 12 episodes of AF in 6 dogs. Seven recordings were not used because one of the MAP signals was lost during a portion of the conversion.

Figure 4 shows an example of the DF and associated ECG, Lt MAP, and Rt MAP in a GS dog with AF for $>250$ seconds that then converts to sinus rhythm after the injection of lidocaine. In these recordings, the DF data over time indicate periods of alternans, tighter clustering of the DF in the LA compared with the RA, and a decrease in DF as conversion to sinus rhythm develops. The decrease in DF corresponds to the increased atrial intervals with abolishment of fragmentation seen on the MAP recording just before the 1st sinus complex. Figure 5 shows a similar case in another GS dog in which conversion of AF required 2 injections of lidocaine. Here, the alterations in the recordings and DF plots indicated a time when conversion almost occurred, but AF resumed. The 2nd bolus of lidocaine then resulted in conversion. Figure 6 shows typical power spectra from the LA and RA during AF, after lidocaine injection, and after cardioversion to sinus rhythm. At the time lidocaine was injected, the DF for the LA was higher, but less broad than in the RA. As the lidocaine took effect, the DF decreased and once conversion occurred, the DFs suddenly shifted to a much lower frequency. Figure 6 also illustrates why the SE was found to be significantly higher in the RA as reflected in the broader peaks. Additionally, the harmonics in the LA compared with the RA indicate that the morphologies of the LA action potentials were more nearly identical than the RA, supporting an increased order in the LA compared with the RA. In sinus rhythm, the number of harmonics was increased.

All DF values for each dog from the point of the injection of lidocaine to the conversion to sinus rhythm are shown in Figure 7. For the DF data, the Huynh-Feldt estimate of Epsilon was 1.000 for both the “time” and “time×side” within-subjects effects virtually identical to the value of the Epsilon parameter under no violation of the sphericity assumption. DF significantly changed in this group of dogs during conversion ($P < .001; F = 4.77, df = 12,60$). Polynomial contrast analysis showed that DF followed a linear trend in time with a negative slope ($P = .002; F = 32.6, df = 1.5$). The significant decrease in DF was identified during conversion although 5 of the 12 episodes of AF had $<100\%$ of the conversion time included (3 episodes 80%, 2 episodes 75%). No significant dog effect was observed ($P = .175; F = 2.44, df = 5.5$). No statistically significant interactions among the factors side, time, and dog were found (all $P$-values $> .19$).

Mean SE was significantly different among dogs ($P = .027; F = 5.76, df = 5.6$). In Figure 7, the SE values over the conversion time are given for all dogs for the LA and RA with the mean values for the LA and RA shown in Figure 8. For the SE data, the Huynh-Feldt estimate of Epsilon was .295 for the “time” and 0.358 for the “time×side” within-subjects effects, indicating a severe violation of the sphericity assumption. Although a decrease in the RA SE is seen (time effect), suggestive of an increase in dynamical organization as the lidocaine takes effect when adjusted for the lack of sphericity relating to the SE responses recorded over time, the change was not statistically significant ($P = .12; F = 1.84, df = 6.2,37.2$). The adverse effect (LA versus RA) was significant ($P = .03$).
In this study of GS dogs with inherited ventricular arrhythmias, the important results are (1) lidocaine converts vagally induced AF to sinus rhythm and (2) during this conversion the DFs of the LA and RA decrease while a dynamical organizational gradient exists between the LA and RA.

Lidocaine converted vagally mediated AF to sinus rhythm in the dogs of this study. Lidocaine usually is not considered a treatment for supraventricular arrhythmias such as AF or AT in dogs. Instead, it most frequently has been used to abolish dangerous ventricular arrhythmias in dogs. Additionally, studies in humans demonstrated that lidocaine was ineffective in converting AF to sinus rhythm. However, recent studies of lidocaine and ranolazine have given mechanistic reasons for reconsidering Na-channel blockers in the treatment and prevention of certain types of AF. Furthermore, an early study by David et al. showed that lidocaine terminated AF in a canine model under conditions of increased parasympathetic tone produced by α-chloroalose anesthesia or direct vagal nerve stimulation. Our results corroborated these findings, although our AF induction methods were less aggressive. We also showed that after treatment with atropine on the background of high vagal tone caused by fentanyl, AT converted to sinus rhythm after treatment with lidocaine. This result concurs with a recent report of lidocaine converting AT in the dog.

Given the above situations of increased vagal tone for which Na-channel blockade is capable of converting AF to sinus rhythm, understanding why increases in parasympathetic tone cause AF may facilitate understanding why lidocaine actually has an antiarrhythmic effect on the atrial myocardium. In our study, fentanyl was the enhancer of vagal tone. Fentanyl is a potent μ-opioid-receptor agonist that increases vagal tone by altering synaptic neurotransmission to cardiac vagal nerves by...
inhibition of presynaptic release of γ-aminobutyric acid (GABA). Increase vagal tone promotes AF by regionally decreasing action potential duration (APD), and subsequently increasing the dispersion of refractoriness. This effect is attributed to the heterogeneous distribution of parasympathetic innervation of the atria, and different
densities of potassium channels (IKr, IKACH) between the LA and RA.  

It may be that only AF that is caused by an increased parasympathetic tone is amenable to conversion to sinus rhythm by lidocaine, but other related drugs with stronger and more preferential effects on atrial tissue may have a more generalized antiarrhythmic effect for AF. A recent study compared the effects of 2 inactivated-state Na-channel blockers, lidocaine and ranolazine. Both drugs produce an atrial-selective depression of Vmax, conduction velocity, diastolic threshold of excitation, and use-dependent postrepolarization refractoriness (PRR). Lidocaine shortens the APD in the ventricles, but not in the atria, whereas ranolazine prolongs late repolarization in the atria and ranolazine has a higher selectivity for the atria. Lidocaine interacts with the autonomic nervous system, most likely at the level of the muscarinic receptors. Relevant to our study, lidocaine and ranolazine blunt the effects of acetylcholine (responsible for the vagal effects on the myocytes). Although ranolazine in the study by Burashnikov et al. was more effective in preventing and terminating AF in a canine model, all episodes of AF were terminated in our study by lidocaine. However, additional channel-blocking properties of ranolazine may give additive benefit to this drug for an antiarrhythmic effect in AF that lidocaine does not share. Therefore, the antiarrhythmic effect of lidocaine demonstrated in our study is likely due to multiple factors including decreasing the effect of acetylcholine and the preferential Na-channel blocking on the atria, which results in decreased excitability and therefore increased PRR.

The effects of Na-channel blockade on individual myocytes contribute to potential antiarrhythmic effects, but so do the summed electrophysiologic properties responsible for the mechanisms of re-entry in generating and maintaining the AF. Re-entry is dependent on conduction velocity, wavelength, and refractoriness. Atrial refractoriness is indeed shortened during vagal stimulation, which decreases the wavelength for re-entry and allows a higher frequency of activation, thus enhancing AF and increasing the DF. A specific type of re-entry mechanism responsible for AF is spiral wave re-entry. In this type of re-entry, a primary “mother rotor” re-entrant wave forms in the left atrium, and drives several re-entrant “daughter waves” in the right atrium. Conversion to sinus rhythm in these studies demonstrated a slowing of atrial electrical activity (DF) and an increase in the organization. DF of vagally induced AF decreases markedly when vagal stimulation is re-
duced or stopped. In our study, the DF of the atria decreased with lidocaine until conversion to sinus rhythm. Furthermore, organization remained prominent in the LA compared with the RA throughout the conversion. This finding could be consistent with the persistence of a “mother rotor” wave in the LA, a more highly organized structure, driving several less-organized “daughter waves” in the RA. Furthermore, the measure we used of RA SE to judge organization during the conversion moved in the direction of increased organization, suggesting progressively more organized “daughter waves” before conversion, although the measure did not reach statistical significance in our experiments.

Limitations

Our study was conducted in a specific breed with known inherited ventricular arrhythmias and infrequent atrial arrhythmias. Although our results may not be applicable to dogs in general, we believe that under specific and acute conditions of AF induction, lidocaine has the potential to convert AF to sinus rhythm. Our results agree with those in other experimental studies of mongrels in which lidocaine was effective in returning AF to sinus rhythm. Furthermore, we have shown clinically that lidocaine given within 1 hour of the development of AF in dogs with vagally induced AF resulted in conversion to sinus rhythm.

Conclusion

Lidocaine converts AF to sinus rhythm in dogs with vagally associated AF induction. Importantly, the discovery of this effective treatment for experimentally induced AF encouraged the successful use of lidocaine for specific clinical situations that cause AF in dogs.

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Footnotes

2. Fentanyl citrate, Hospira Inc., Lake Forest, IL
3. Nembutal, Abbott, Chicago, IL
4. Baxter Healthcare Corporation, Deerfield, IL
5. BioPac Systems, Model MP 150, AcqKnowledge 3.7.3, Santa Barbara, CA
6. EP Technologies, Sunnyvale, CA
7. Bloom Stimulator, Fischer Imaging Corp, Denver, CO
8. Atropine, Vedco, St Joseph, MO
9. Lidocaine, Vedco
10. MatLab (version 6.5), the Math Works Inc, Natik, MA
11. SPSS 15.0, SPSS Inc, Chicago, IL

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