An Acute Experimental Model Demonstrating 2 Different Forms of Sustained Atrial Tachyarrhythmias

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Background—The objective of this study was to develop an acute experimental model showing both focal and macroreentrant sustained atrial fibrillation (AF).

Methods and Results—In 31 anesthetized dogs, bilateral thoracotomies allowed the attachment of electrode catheters at the right and left superior pulmonary veins, atrial free walls, and atrial appendages. Acetylcholine, 100 mmol/L, was applied topically to either appendage. Sequential radiofrequency ablation was achieved for the ganglionated plexi (GP), found adjacent to the 4 pulmonary veins. In 12 separate studies, a propafenone bolus, 2 mg/kg, was given before and after GP ablations at the start of acetylcholine-induced AF. Acetylcholine caused abrupt onset of AF (n=22) or induced AF by burst pacing (n=9) that lasted ≥10 minutes. Rapid, regular, or fractionated atrial electrograms were consistently seen (average cycle length, 37±7 ms) at the appendages versus cycle lengths of 114±23 ms at other atrial sites. After ablations of GP, AF abruptly terminated (n=25). In 6 dogs, sustained atrial tachyarrhythmias continued. Pacing at specific atrial sites organized electrograms of one atrium or also captured the other atrium. The latter resulted in termination when pacing was stopped in 4 of these 6 experiments. Propafenone did not change the duration of focal AF before GP ablation (17±9 versus 14±8 minutes; control, P=0.6) but terminated reentrant atrial tachyarrhythmias (12±3 versus 2±1 minutes, P=0.0009).

Conclusions—Before GP ablation, acetylcholine (100 mmol/L) induced sustained AF characterized by rapid, focal firing. GP ablations were associated with loss of focal firing and regularization of electrograms in both atria before termination. Propafenone failed to terminate focal AF but rapidly terminated entrainable macroreentrant atrial tachyarrhythmias. (Circ Arrhythmia Electrophysiol. 2009;2:384-392.)

Key Words: atrial fibrillation ▪ autonomic nervous system ▪ atrial tachyarrhythmia

Over several decades in the last century, there was a continuing controversy regarding the mechanism underlying atrial fibrillation (AF). In 1947, Scherf2 showed that injection of aconitine into the atrial appendage in the dog heart induced atrial tachyarrhythmias (ATa). This rapidly firing area could be isolated within the appendage by applying a clamp between the appendage and the rest of the atrium. In 1950, Scherf et al2 found that the most effective method for inducing sustained AF was the topical application of a solution of acetylcholine (ACh) to the area of the sinus node or atroventricular junction. Local cooling of these areas suppressed the arrhythmia. Scherf concluded that “the presence of a focus must be assumed.”

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In 1959, Moe and Abildskov stated, “It is . . . difficult to believe [that an ectopic pacemaker] would be endowed with sufficient stability to persist for years as fibrillation often does.”3 Their further investigations in 1964, using computer modeling, led them to hypothesize the existence of multiple wavelets constituting macroreentrant circuits that were self-sustaining during AF and provided maintenance for the arrhythmia.4 Subsequently, elegant mapping studies in experimental animals by Allessie et al5 established the predominant view that multiple macroreentrant circuits were the mechanical basis for AF.

The clinical findings of Jais et al6 and Haissaguerre et al7 resurrected the focal theory. The Bordeaux group discovered that in a majority of their patients with paroxysmal forms of AF, rapid focal firing arising from the pulmonary vein myocardium was responsible for initiating and possibly maintaining the episodes of AF.

The purpose of the present study was to demonstrate that the 2 different forms of AF, focal and macroreentrant, can be
ganglionated plexi (GP) were designated as follows: the anterior
anteroposterior aspect of the LIPV; and the ligament of Marshall at its
to the coronary sinus (Figure 1). Electrical stimulation at
connections to the coronary sinus (Figure 1). Electrical stimulation at
spontaneous” AF did not occur within 2 to 5 minutes, AF
right (AR) GP situated between the caudal end of the sinoatrial node
the RSPV; the inferior right (IR) GP located at the junction of the
the ACh, which was not induced
LAA. If “spontaneous” AF did not occur within 2 to 5 minutes, AF
a bolus. The duration of AF was again determined.
ablation of the GP, there were multiple applications of ACh to induce
Definition of Terms
Spontaneously Occurring AF
An abrupt onset of AF occurred several minutes after the topical
application of ACh to the atrial appendages, which was not induced
Sustained AF
Before GP ablations, sustained AF was defined as irregular ventricular
responses and atrial activations whose mean rates were ≥500/
min lasting for ≥10 minutes. During sustained AF, several different
electrogram morphologies were identified (Figure 2) similar to those
described previously.12
Type I
Type I electrograms are discrete, regular electrograms with relatively
long isoelectric intervals.
Type II and Type III
Type II and type III are fractionated electrograms with 2 or 3
deflections; both type II and III show isoelectric intervals, albeit short.
Methods
In 31 adult mongrel dogs anesthetized with sodium pentobarbital (30
mg/kg), a right and left thoracotomy allowed the attachment of
multi-electrode catheters to right and left superior pulmonary veins
(RSPV, LSPV), the right and left atrial free walls (RA, LA), and their
appendages (RAA, LAA). In addition, a polyethylene tube was
attached to the RAA and LAA as a barrier between the AA and the
rest of the atrium (Figure 1, A and B). A line of tissue glue was
attached to the RAA and LAA as a barrier between the AA and the
rest of the atrium.
identified by various means within a single acute experimental
model.
Procedures
To induce sustained AF (≥10 minutes), a gauze pad moistened with
acetylcholine (ACh) (100 mmol/L) was applied to the RAA or
LAA.6 If “spontaneous” AF did not occur within 2 to 5 minutes, AF
was induced by mechanical or electrical stimulation applied to the AA.
During AF, the various morphologies of electrograms were charac-
terized based on the definitions detailed below. Anatomically, the
ganglionated plexi (GP) were designated as follows: the anterior
anterior pulmonary veins and on the right atrial free wall and right
atrial appendage. A polyethylene tube was sutured across the
RAA, and tissue glue was used to create a leak-proof barrier. A
gauze pad moistened with ACh was then applied to the RAA
(hatched area). B, A similar arrangement of electrode catheters
was made on the left PVs LA and LAA, as well as the plastic
barrier so ACh could be applied on the LAA. SVC indicates
superior vena cava; ARGP, anterior right ganglionated plexi; IRGP,
ierior right ganglionated plexi; LPA, left pulmonary artery; RV, right ventricle; LV, left ventricle;
SLGP, superior left ganglionated plexi; LOM, ligament of Mar-
shall; ILGP, inferior left ganglionated plexi.

Figure 1. Diagrammatic representation of the atria as seen from
a right- or left-sided thoracotomy. A, On the right side, elec-
trode catheters were sutured at the right superior and right in-
ferior pulmonary veins and on the right atrial free wall and right
atrial appendage. A polyethylene tube was sutured across the
RAA, and tissue glue was used to create a leak-proof barrier. A
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right (IR) GP located at the junction of the
inferior vena cava and the atria; the superior left (SL) GP located
adjacent to the base of the LSPV; the inferior left (IL) GP at the
posterior aspect of the LIPV; and the ligament of Marshall at its
connection to the coronary sinus (Figure 1). Electrical stimulation at
these sites has been described previously in reports from our
laboratory.9–11 Briefly, the stimulation parameters were: frequency,
20 Hz; duration of each stimulus, 0.1 ms; voltage, 0.6 to 3.2 V. These
voltages were below the threshold for atrial excitation but induced
progressive slowing of the sinus rate. Progressively higher voltages
induced AF with increasing degrees of atioventricular block leading
to marked slowing of the ventricular response. Subsequently, radio-
frequency energy (maximum, 15 W) was applied by direct visual
to each identified site with the Isolator Transpolar Pen
(AtriCure, Inc, Cincinnati, Ohio). This is a handheld probe with
a 5-mm-wide tip. Two 1-mm-wide, 8-mm-long electrodes separated
by 3 mm of insulation are located on the tip of the pen. Radiofre-
cency energy is driven between the 2 electrodes. During energy
delivery, a sensing unit adjusts energy delivery by determining
online measurements of tissue conductance every 20 ms during
ablation. The ablation procedure was performed in 2 separate stages,
first on one side (via right or left thoracotomy) and then on the other
side using the same method of ACh application on one or the other
AA. We delivered multiple burns (range, 3–5) over each site, causing
blackening of the fat pad tissue.
Successful ablation of the GP was determined when electrical
stimulation at the GP failed to induce heart rate slowing during sinus
rhythm or induced AF. Because of the time required for bilateral
ablation of the GP, there were multiple applications of ACh to induce
and sustain AF.
Drugs Administration
In a separate group of 12 dogs, the effects of a bolus dose of 2 mg/kg
propafenone was determined on the AF or ATa induced by ACh
application to the AA. In the baseline state, 100 mmol/L ACh was
initially applied to the AA, and the duration of spontaneous or
electrically induced AF was registered. After flushing the AA with
saline, a second application was made. When the focal form of AF
was induced, 2 mg/kg propafenone was injected intravenously as a
bolus. The duration of AF was again determined.
Subsequent to GP ablations via left and right thoracotomies, AF
was induced after application of ACh to the AA and burst pacing.
The duration of AF was again determined. After spontaneous
termination and flushing with saline, a second ACh application
was made on the AA, allowing AF reinduction. The same dose of
propafenone was again injected, and the duration of AF/ATa was
noted. At least 2 hours elapsed between the 2 doses of propafenone
before and after GP ablations.

Figure 1. Diagrammatic representation of the atria as seen from
a right- or left-sided thoracotomy. A, On the right side, elec-
trode catheters were sutured at the right superior and right in-
ferior pulmonary veins and on the right atrial free wall and right
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shall; ILGP, inferior left ganglionated plexi.
Rotor-Like Electrograms

Rotor-like electrograms have very rapid (with almost no isoelectric intervals) regular activation with a relatively constant amplitude and cycle length (CL) ranging from 25 to 50 ms. Although the morphology of these electrograms was similar to those reported by others using different methodologies, the underlying mechanisms may differ.

Entrainment

Rapid atrial pacing during AF at a right or left atrial site induced local capture of an adjacent electrogram only (local entrainment). After GP ablations, overdrive pacing at sites showing type I electrograms captured the electrograms recorded in the ipsilateral atrium (regional entrainment) or captured the electrograms recorded on both atria (contralateral entrainment).

ATa

We used the designation ATa for the tachyarrhythmia that continued in 6 of 31 dogs after GP ablations or that was induced by the application of 100 mmol/L ACh to the AA in the propafenone study also after GP ablations. We address the difficulty in differentiating between AF and atrial tachycardia (AT) in the Discussion section.

Guidelines for Animal Care

All experiments were approved by the Institutional Animal Care and Use Committee of the University of Oklahoma and the Veterans Affairs Medical Center. The animals were housed at the Animal Research Facility at the Veterans Affairs Medical Center.

Statistical Analysis

The data are expressed as mean±SD. ANOVA, 2-way analysis for repeated measures, was used for comparison of data within 2 groups with and without propafenone administration. Probability values of ≤0.05 were considered statistically significant.

Results

In the baseline state, before ACh application, burst atrial pacing induced AF whose duration ranged from 9 to 40 seconds. Within 2 to 5 minutes after ACh was applied to the AA, sustained AF (≥10 minutes) occurred spontaneously in 22 of 31 dogs or was induced electrically in 9 of 31 dogs. AF was, in most cases, characterized by rotor-like electrograms (average CL, 37±7 ms) at the AA and a relatively longer CL (type I electrograms) at other atrial sites (average CL, 114±23, P=0.01). However, only in those dogs showing spontaneous AF were CFAE observed at the right and left PV recording sites.

Figure 2 shows a typical example of the spontaneous initiation of AF after topical application of ACh (100 mmol/L) on the RAA. A premature atrial beat (asterisk) with short coupling to the preceding sinus beat initiated very rapid, rotor-like electrograms at the same site (RAA) from which the earliest ectopic beats arose. Note the greater rapid firing (rotor-like electrograms) at the RAA (CL, ~50 ms). The other recorded atrial sites showed type I electrograms (average CL, 100 ms; RIPVD2) or mixtures of morphologies, for example, type II (LIPVD2) and type III, (LSPVD2, arrow). Other sites (RAD2) showed CFAE (arrows, toward the end of that trace).

In another case in which ACh was applied to the RAA, the induced AF (Figure 3A) showed CFAE at RAA recordings and were observed at other sites on the atria, for example, LAAD2. In Figure 3B, after ablation of the ARGP and IRGP (Figure 1), there was organization of the electrogram morphologies toward type I, particularly at the LSPV, LA, and RSPV recording sites. After ablation of the SLGP, LOM, and IRGP (Figure 3C), further organization was noted during ongoing AF such that synchronization of the sequence of activation of the recorded electrograms from the LAA to the RAA was observed. Moreover, the same CL was measured across 10 cycles (1024 ms) in both the left and right atria. Note the irregular/irregularity of the R-R intervals during this tachyarrhythmia.

In 25 of the 31 dogs, after GP ablations (both sides), a consistent pattern of organization and atrial synchronization (Figure 3C) was followed by abrupt termination of AF and restoration of sinus rhythm. In Figure 4, rapid and irregular activity in the RAA recordings abruptly converted to all of the recorded electrograms manifesting the same sequence of activation (last 2 electrogram traces) before AF abruptly terminated. It should be noted that the R-R interval in the last 4 beats (ECG) were essentially the same (236 ms), indicative of an AT with 2:1 block; yet, the right and left atrial electrograms showed different
CLs and activation sequences. This result will be discussed below in regard to differentiating AF from AT.

Figure 5 illustrates another form of sustained ATa that continued after GP ablations in 6 dogs. It should be noted that at the RAA sites (where ACh had initially been applied), relatively rapid, fractionated activity was observed, but the CL was longer than that seen before GP ablations (compare with RAA recordings in Figure 3A). Between these periods of irregular firing, intermittent periods of organization and synchronization of atrial activity were observed, with electrograms from LAA to RAA showing equal CLs over a 9-cycle run (1042 ms). However, the RA electrograms were not synchronized (1018 ms), and more rapid and irregular activation resumed toward the end of the tracings at the RAA, where the ACh had been applied. Also note the irregularity of the R-R intervals throughout. Again, these results will be discussed below.

Figure 6A illustrates that during ongoing ATa with irregular/irregular R-R intervals, atrial pacing at RAA34 at an average CL=116 ms initially captured a large area of the ipsilateral atrium and PVs (regional entrainment),\(^\text{15}\) whereas the LA and LAA recording sites were not entrained. In Figure 6B, during continuing pacing as shown in Figure 6A, synchronous capture of atrial sites in both atria resulted in contralateral entrainment. Subsequent cessation of pacing was followed by termination of the tachyarrhythmia and restoration of sinus rhythm. Pacing-induced contralateral entrainment was followed by termination of the tachyarrhythmia in 4 of these 6 cases.

**Effect of Propafenone Before and After GP Ablations**

The table summarizes the comparative mean values for the duration of AF induced by the application of 100 mmol/L ACh to the AA in the control state compared with the same duration after the administration of a bolus dose of 2 mg/kg propafenone, given before and after GP ablation in 12 dogs. Before GP ablation, there was no significant difference in the induced AF duration with (17±8 minutes) or without (14±8 minutes) the drug administration (\(P=0.6\)).

In contrast, after GP ablations, the same method for inducing AF showed a duration of 12±3 minutes (not significantly different than before GP ablation, \(P=0.4\)) without drug but a significantly shorter AF duration after propafenone administration (2±1 minute, \(P=0.001\)). In these cases we attempted to reinduce AF with burst pacing (×3); the average duration of AF was 16 seconds.
We also determined the effect of propafenone on prolongation of the CL, during AF, at the site at which ACh was applied, for example, the LAA or RAA. Before GP ablations, the mean electrogram CL increased significantly from 31±5 ms to 57±12 ms (P=0.02) as the result of propafenone administration. Yet there was no significant change in the duration of ACh-induced AF. On the other hand, after GP ablations, 100 mmol/L ACh applied to the AA was also effective in inducing firing leading to sustained AF (12±3 minutes). However, the mean electrogram CL was significantly slower (46±11 ms, P=0.01) compared with that measured before GP ablations (31±5 ms). Moreover, the degree of slowing induced by propafenone was also significantly greater (73±11 ms) after than that observed before GP ablations (57±12 ms, P=0.03).

Discussion

Major Findings: ACh Application to the AA
In the present study, using an acute experimental model similar to that described by Scherf et al,1 we were able to confirm that the most rapid source of firing inducing AF was arising from the site at which ACh was applied to the atrium. In addition, we extended the findings of Scherf et al by showing that ablating the GPs could terminate the focal form (n=25) and unmask macroreentrant circuits (n=6). The results of the present study show that rotor-like electrograms and CFAE were consistent features of the electrogram morphologies recorded during spontaneous or induced focal AF with 100 mmol/L ACh applied to the AA. The rotor-like electrograms showed the shortest measurable CL, with the earliest ectopic beats arising at the AA (Figure 2), indicative of a focal ectopic site triggering AF. Other studies have indicated that under these same circumstances, that is, ACh-induced AF, the electrograms recorded at the AA exhibit the highest dominant frequency and a regularity index closest to 1.0.17 In patients undergoing PV isolation, Takahashi et al18 found that vagal excitation shortened the CL of PV activity and increased the incidence of CFAE (see Figure 3, Reference 18).

Figure 4. Spontaneous termination of AF after right- and left-sided GP were ablated. Rapid and irregularly firing activity at the RAA, abruptly converted to atrial synchronization of the recorded electrograms manifesting the same sequence of activation (last 2 beats) before AF termination and restoration of sinus rhythm. Note that the R-R intervals (ECG) of the last 4 beats show essentially the same CLs, consonant with initiation of AT (see Discussion section).

Figure 5. Illustration of an interspersed period of atrial synchronization during ongoing ATa observed in 1 of the 6 dogs that did not terminate after GP ablations. Between periods showing rapid, irregular firing at the recorded RAA sites (where ACh had been applied) there was an intermittent period of organization and synchronization of atrial activity, with electrograms from LSPVd2 to RAA78 showing equal CLs over a 9-cycle run (1042 ms). However, the RA electrograms were not synchronized (1018 ms), and the more rapid and irregular activation resumed at the end of the tracing. See text for further discussion.
Effects of GP Ablations

With stepwise ablation, there was a consistent pattern of regularization of the recorded electrograms from both the atria and the PVs. This organization resulted in the loss of rotor-like electrograms and CFAE and a progression toward type I electrograms (Figure 3, A through C). A similar sequence of events has been reported clinically. Schmitt et al.19 specifically targeted CFAE in a series of patients undergoing radiofrequency catheter ablation. Using an average of 80 radiofrequency applications, these investigators found a regularization of the electrograms in 84% of the 66 patients studied and termination of AF in 42%. Although the present study in dogs cannot be considered comparable, we nevertheless found that regularization and AF termination occurred in 81% (25/31) of cases, with as few as 5 to 10 radiofrequency applications localized to the GP sites. It should be noted that electrogram organization occurred immediately after GP ablation. In some cases, the electrograms distant from the site of GP ablation regularized, as shown in Figure 3, A through C. In this case, ablation of the “right-sided” GP, that is, ARGP and IRGP, resulted in loss of CFAE in electrograms recorded from the LAA. These findings are consonant with our previous studies showing the highly integrated nature of the neural network connecting the various GP.20 A possible explanation for GP ablation leading to electrogram organization may reside in the recent findings by Lin et al.21 They demonstrated, during sustained AF, that concentrations of ACh, applied locally to a bipolar recording a type I electrogram, could convert it to intermittent CFAE (10 mmol/L) or continuous CFAE (100 mmol/L). The ablation of the GP would then be the converse of this effect, whereby ACh released from activated GP would be prevented or attenuated, which in turn would convert CFAE into more organized electrogram morphologies.

Previous Animal Models of AF

The basic study by the Netherlands investigators showing that “atrial fibrillation begets atrial fibrillation”22 by long-term rapid pacing in the goat was later reproduced by Li et al.23 whose mapping studies showed that macroreentrant or multiple reentrant circuits were the mechanism underlying the AF in this model. In a recent report, Chou et al.24 studied...
sustained AF induced by long-term rapid atrial pacing in dogs (74±46 days). They found evidence that both intermittent focal discharges from the PVs and reentry at the PV atrial junctions could be distinguished. Ibutilide, which prolongs refractoriness, was effective in terminating the reentrant arrhythmia but not the focal discharges, suggesting that the latter were “due to a nonreentrant mechanism.” A separate series of 12 dogs with ACh-induced AF, in the present study, were administered propafenone (2 mg/kg), which slowed conduction when administered before and after GP ablations (Table 1). As with ibutilide, propafenone was ineffective in decreasing the duration of focal AF before GP ablations but was consistently effective against macroreentrant ATa/AF induced after GP ablations.

Subsequent to GP ablations, 100 mmol/L ACh applied to the AA also resulted in sustained ATa/AF (Table 1); however, the average CL of the local firing was significantly longer than that seen at the same AA sites before GP ablations. Thus, the administration of the same propafenone dose caused a significantly greater slowing of conduction than that seen before GP ablation with rapid termination of ATa/AF (2±1 minute). An apparently contradictory finding was reported by Chou et al,25 who found that a similar class I agent, procainamide, also reduced the rate of focal discharge in a long-term pacing model of sustained AF. However, 5 of 6 instances of focal discharge–based AF were terminated.

It is interesting to note that the CL of the focal discharges measured in this report was almost 3 times longer than those recorded in the present study in the baseline state. Our data suggest that the longer the initial CL of the focal discharges, the greater the chance that further slowing of conduction with a type I agent will lead to AF termination. The differences in the CLs between those found by Chou et al and the present study may be explained by the differences in the experimental models used to induce the sustained focal discharges.

Distinguishing AF From AT

Before GP ablation, the electrograms were characterized by rotor-like activity and CFAE, which only allowed local entrainment of closely adjacent sites, particularly those few sites showing type I electrograms, whereas after GP ablation, in those 6 cases in which a tachyarrhythmia continued, atrial synchronization- or pacing-induced entrainment showed regional (Figure 5) and contralateral capture (Figure 6A, Figure 6B, respectively).

In this regard, Chugh et al26 studied 85 patients with macroreentrant AT after AF circumferential ablation. AT was defined as “a regular, supraventricular rhythm . . . and a consistent atrial activation pattern.” That the ECG was not used for this definition is shown by the irregular R-R intervals in the rhythm strips of a typical AT patient (Figure 2, Reference 26). Moreover, the authors further indicate that it was unlikely that AT was AF “because every AT . . . was entrainable. AF . . . would not be expected to be entrainable.”

In the present study, we found it difficult to distinguish AF from AT in those cases in which the tachyarrhythmia continued after GP ablation. Using either the ECG or as many as 14 biaxial and PV recording sites, neither one nor the other provided a definitive method for differentiating AF from AT. Specifically from the regularity of the R-R intervals in the ECG alone in Figure 4 (last 4 beats), the rhythm could be designated as AT with 2:1 atrioventricular block. However, the RAA electrograms show either CFAE or markedly irregular atrial activation. Furthermore, there is no atrial synchronization between left and right atria. In contrast, Figure 3C shows atrial synchronization in all recorded electrograms, but there is marked irregularity of the R-R intervals in the ECG. Yet, in all of these cases, either regional or contralateral atrial synchronization and/or pacing-induced entrainment was demonstrated, suggestive of macroreentrant circuits. A strict definition of AT would require an essentially regular R-R interval on the ECG as well as regular and synchronized atrial electrograms from multiple recording sites in both atria and PVs. Therefore, the rhythms encountered after GP ablation in the present study were designated as ATa.

Coexistence of Focal and Macroreentrant Forms of AF

Although Moe and Abildskov3 promulgated the widely accepted theory that AF was caused by a reentrant mechanism, they stated in their 1959 article as follows: “We may further conclude that true fibrillation may be self-sustaining and independent of whatever initiating agency . . . [however] It is conceivable that all possible mechanisms are encountered in the clinic.” Even Allessie et al,3 whose elegant experimental studies provided verification of the multiple wavelet hypothesis, raised a similar caveat: “the two classic explanations for fibrillation, ie, multiple rapidly discharging foci and multiple reentry, are not mutually exclusive.” It seems quite conceivable that in cases in which AF continues for many years, both

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<th>Table. Propafenone Effect on Durations and CLs of Focal Versus Reentrant AF</th>
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<td><strong>Before GP Ablations (Focal AF)</strong></td>
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| Ach AF Duration, min  | Propafenone Ach AF Duration, min  | Baseline CLs  | CL After Propafenone  | Cap 
| Average  | 14  | 12  | 2  | 46  | 73  |
| SD      | 8   | 9   | 5   | 12  |      |
| P value | 0.6* | <0.05† | 0.0009‡ | 0.01§ | 0.03|
mechanisms act together. In the present study, after GP ablations, the sustained tachyarrhythmia was characterized by rapid irregular activity coming from the AA, the initial focal firing site, yet synchronization and entrainment of large areas of the atrium indicated the coexistence of the 2 mechanisms ascribed to AF. The use of pacing-induced entrainment, particularly the contralateral form, allowed us to control the rhythm and in some cases terminate the tachyarrhythmia. During some episodes of pacing-induced contralateral entrainment, we noted the abrupt occurrence of more rapid firing and irregular electrograms at 1 or more sites that interrupted the capture of both atria, reverting the arrhythmia from a macroreentrant circuit to a regional form of entrainment. However, with continuation of pacing, this response again reversed itself. These instances were indicative of a focal site intermittently competing with a macroreentrant circuit for control of the arrhythmia. When pacing was terminated during contralateral entrainment, pace termination could be achieved. This was not the case during regional entrainment.

**Clinical Implications**
PV isolation has become the most accepted method of treatment for focal AF, including the paroxysmal, persistent, or chronic forms. However, several published studies reported that the relatively long-term success of PV isolation has varied from 70% to 80% for paroxysmal and persistent cases to 50% to 60% for chronic forms. Other lesions sets have been performed to ablate CFAE and areas within the coronary sinus and the superior vena cava. Nevertheless, end points for determining when enough lesions have been applied has differed among clinical electrophysiologists; for example, some have chosen to cardiovert to sinus rhythm if after the many lesion sets have been completed but AF continues. Others, after sinus rhythm is achieved, have required noninducibility in response to burst pacing or premature beats (inducing AF ranging from <30 seconds to <3 minutes).

In the clinical setting, GP ablation has been accomplished either purposefully or inadvertently during the course of PV isolation. Thus, it seems feasible to attempt to entrain by pacing if regularization manifests as PV isolation procedures progress. Moreover, if sinus rhythm is achieved and burst pacing induces AF lasting several minutes, a standard antiarrhythmic drug (class IC or type III), particularly one that failed previously, can be administered in an attempt to terminate and prevent reinduction of AF. Such a procedure has been shown to be effective in a small number of clinical cases after CFAE had been ablated.

**Limitations**
Although contralateral entrainment was followed by pace termination in 4 cases, in 2 cases, despite initial contralateral entrainment, there was resumption of focal firing and ATa/AF. In these 2 cases, more extensive mapping might have revealed nontreated focal or CFAE sites responsible for continuation of the tachyarrhythmia. Thus, a focus or another reentrant circuit, with sites not being registered, could infiltrate the entrained circuit causing the asynchrony and reinduction of irregular firing and ATa/AF (Figure 5) when entraining pacing ceased. Nevertheless, the ability to pace-terminate in 4 of 6 cases would indicate that a sufficient number of sites were captured in those instances, so that termination of the ATa would result when pacing terminated.

It should be noted that in the present study, there were time delays between GP ablations and repeated applications of 100 mmol/L ACh, which were required to initiate and sustain AF. Because the effects of ACh tended to decrease with time, supposedly because of hydrolysis by tissue cholinesterases, the timing of the bilateral GP ablation and ACh application varied. Thus, the continuation of ATa/AF in the 6 dogs, after GP ablation, could have been caused by the fortuitous application of ACh close to the time of the last GP ablation. Also, the small number of dogs in whom AF continued after GP ablations precluded a more quantitative evaluation of the entrainment phenomenon.

**Conclusions**
With the major GP intact, ACh (100 mmol/L) applied to the RAA or LAA resulted in spontaneous (22/31) or electrically induced (9/31) sustained AF with focal triggering (rapidly firing, rotor-like electrograms; CL range, 25 to 50 ms) arising at the AA. In addition, there were associated CFAE recorded at the majority of biatrial and PV sites. Pacing induced only local entrainment, and propafenone administration was not effective in terminating focal AF. Subsequent to GP ablations, rotor-like electrograms and CFAE were absent and replaced by more organized electrogram morphologies (types I through III) followed by AF termination. In 6 of 31 cases in which the tachyarrhythmia continued, pacing-induced entrainment (regional and contralateral) of the ATa could then be achieved, leading to termination of the putative macroreentry mechanism in 4 of 6 experiments. Also, propafenone was consistently effective in terminating these macroreentrant--based tachyarrhythmias.

**Acknowledgments**
We thank Mrs Andrea Moseley for secretarial and technical assistance and Joseph Klimkoski and Dr Tushar Sharma for aid in the preparation of these experiments.

**Sources of Funding**
This study was supported in part by a grant from the American Heart Association (0650077Z, S.S.P.) and the National Heart, Lung, and Blood Institute (5K23HL069972, S.S.P.); a grant from St. Jude Medical; and by the Helen and Wil Webster Arrhythmia Research Fund (B.J.S.).

**Disclosures**
Dr Scherlag is a consultant for AtriCure, St Jude Medical, AF Division, and Symphony Medical; research funding was provided by St Jude Medical, AF Division, Cardiovascular Therapeutics; Dr Lazzara is a consultant for Sanofi-Aventis, CardioMEMS, Reliant Pharmaceuticals, and CV Therapeutics; and Dr Jackman is a consultant for Biosense Webster, Stereotaxis, ProRhythm Inc, CardioFocus, EndoSense, and AtriCure.

**References**


CLINICAL PERSPECTIVE

An acute experimental preparation has been developed which demonstrates that 2 distinct forms (focal and macroreentrant) of atrial fibrillation can be identified before and after ablation of several of the autonomic ganglia adjacent to the pulmonary veins. Clinically, pulmonary vein isolation has become the most accepted method of treatment for focal atrial fibrillation; however, there has been no consensus as to the end points for the ablation procedure. We have shown that the same propafenone dose can readily terminate macroreentrant atrial fibrillation whereas it is ineffective in the focal form. Moreover, the former can be entrained leading to pace termination. These same methods may be useful as end point determinants in patients undergoing atrial fibrillation ablation procedures.
An Acute Experimental Model Demonstrating 2 Different Forms of Sustained Atrial Tachyarrhythmias
Guodong Niu, Benjamin J. Scherlag, Zhibing Lu, Muhammad Ghias, Yuan Zhang, Eugene Patterson, Tarun W. Dasari, Soni Zacharias, Ralph Lazzara, Warren M. Jackman and Sunny S. Po

Circ Arrhythm Electrophysiol. 2009;2:384-392; originally published online April 24, 2009; doi: 10.1161/CIRCEP.108.810689
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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