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成年豬持續性心房顫動的時間與空間頻幅分析：

顫動激發中心之研究

Spatial-Temporal Frequency Analysis of Spontaneous Sustained Atrial Fibrillation in a Swine Model: The Search of Active Rotors and Modification by Various Interventions

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Introduction

Traditionally, atrial fibrillation has been recognized as an arrhythmia made of endless reentrant wavelets. Evidences supporting the reentry mechanism arose originally from the computer simultation study by Moe et al (1), and subsequently supported by activation sequence mapping study by Allessie et al. The seemingly ever-emerging reentrant wavelets have a spiral wave rotor, a migrating course of propagation and continuous transformation or degeneration into daughter wavelets with or without wavefront collisions (2, 3). In recent years, however, the multiple wavelet theory has been challenged by the concept of rotor firing and fibrillatory conduction proposed by Jalife et al (4-6). Meanwhile, recent clinical studies have reported successful ablation of focal atrial fibrillation at the pulmonary veins in some young patients (7, 8). The de novo idea of pulmonary vein triggers have also been extended to all atrial fibrillation patients, be it acute or chronic, paroxysmal or persistent and confronted with highly variable therapeutic outcome (7-9). Experimental studies from Jalife et al have substantiated the rotor concept by showing that the activation frequency in the left atrium, particularly around the pulmonary veins or at the posterior wall, is more dominating than that in the right atrium. Cryothermal or radiofrequency energy delivered at the pulmonary orifices or at the left atrial posterior wall can terminate and prevent the sustenance or recurrence of atrial fibrillation. As mentioned previously, despite the initial success in catheter ablation, recurrence of atrial fibrillation following the pulmonary vein-based radiofrequency intervention is gradually increasing from less than 10% to over 60% (7-9). More aggressive pulmonary vein isolation protocol is developed and undergoing more broadspectrum human studies. Yet, long- or even mid-term results are lacking. Surgically, direct radiofrequency or cryothermal circumferential ablation with compartmentational lines (10-13) has nevertheless sustained the maintenance of

sinus rhythm and adequate atrial mechanical function in over 80% of the patients for over 5 years. The discrepancy between various interventional strategies is evident and underlying causative factors are unknown.

The protocol of the present study is attempting to delineate the possible existence of driving rotors in a porcine model of persistent atrial fibrillation by relevant activation sequence analysis and frequency component evaluation. The mathematical results will be challenged by two categoric drugs, i.e. sodium channel blocking propafenone and potassium channel blocking sotalol, as well as by intentional cryoablation technique. The hypothesis stated that the driving rotor and the relevant left-to right gradient of activation frequency will not be affected by propafenone nor sotalol, and the isolation of driving rotors will "regularize" the activation sequences in the remained atrial tissue, which may terminate the persistent atrial fibrillation.

Methods and Materials

Study animals

Twenty-eight adult pigs of Yorkshire-Landrace strain were used. The mean body weight was 75 ± 14 kg (range 60 to 94 kg). The experimental protocol conformed to the *Guide for the Care and Use of Laboratory Animals* (NIH Publication No. 85-23, revised 1996) and approved by the Institutional Animal Care and Use Committee of the National Taiwan University College of Medicine. All pigs were provided by and housed at the animal facility in the Pig Research Institute in Taiwan (PRIT) in Chunan, Taiwan. The animal experiments were conducted at the PRIT (pacemaker insertion) and in the animal catheterization laboratory at the National Taiwan University Hospital (electrophysiological studies and mapping).

Sustained atrial fibrillation induced by rapid atrial pacing

Of the 28 pigs, 25 were entered into the study group and 3 in the sham group to

serve as a control. Baseline surface 12-lead ECG and transthoracic echocardiography were performed to evaluate cardiac function and to exclude any animals associated with cardiac abnormality. Under intravenous anesthesia by thiamylal (2-3 mg/kg) (Kyorin Pharmaceutical Co., Tochigi, Japan) or ketamine (1-2 mg/kg) (Shin-Tong Pharmaceutical Co., Taoyuan, Taiwan), each animal was transvenously implanted with either a high-speed atrial pacemaker (Itrel-II and Itrel-III, model 7424 and 7425, Medtronic, Inc., Minneapolis, Minnesota, U.S.A) for the study group or an inactive pacemaker for the sham group. The atrial pacing lead (Model 4568, Medtronic Inc.,) was inserted via the left internal jugular vein by a cut-down technique and screwed to the right atrial appendage or the right anterior atrial wall under fluoroscopy. Pacing threshold, impedance and P-wave amptitude of the atrial lead were tested before connecting to the pacing generator which was implanted subcutaneously in the neck and below the chin of the pig. After closure of the pacemaker pocket, the animal was left recovering from anesthesia and returned to the pig housing dormitories. Three days later, the atrial high-speed pacemaker was programmed to a rate of 600 beats per minute (bpm) for a total of six weeks. Oral digoxin (0.25mg per day) was given daily from the first day after pacemaker implantation to minimize a rapid heart rate response and possible congestive heart failure. Consistency of the atrial pacing was regularly checked daily in the first week and weekly thereafter by a portable ECG monitor.

Electrophysiological mapping study

After six weeks of continuous pacing, the atrial pacemaker was turned off by a telemetry programmer. Transthoracic echocardiography was repeated to evaluate the changes of cardiac function. Subsequently, animals underwent electrophysiologic mapping studies in a random order in day 1, day 2, or day 3 after termination of atrial pacing.

Each animal was intubated via tracheostomy and ventilated artificially by a modified Harvard respirator (tidal volume 10-15 ml/kg, respiration rate 20-25/min) after full sedation with intravenous thiamylal (initial 5 mg/kg, then 50-100 mg intermittently). Right thoracotomy was performed and the pericardium was cradled to expose the atrial free surface.

Epicardial mapping of activation sequences of AFib was performed by a rectangular recording plaque electrode (62×52 mm^2) (Prucka Engineering Inc., Houston, Texas, U.S.A), which contains 224-site bipolar recordings by paired connections. The intra- and inter-bipolar distances were 3.5 mm. The epicardial mapping was conducted sequentially on the right and the left atrium. All 224-site atrial local electrograms and surface ECG were monitored and recorded simultaneously by a computerized multi-channel mapping system (CardioMapp^{TM}, Prucka Engineering Inc.). The data were acquired at 1000 samples per second. Each event was recorded continuously for 30 seconds.

Pharmacological study

Intravenous dl-sotalol (1.5 mg/kg) (Bristol-Myers-Squibb GmbH, Munich, Germany) or propafenone (2 mg/kg) (Knoll SA, Liestal, Germany) was given in 11 animals (sotalol in 6, propafenone in 5) to assess the drug effects. Both right and left atria were re-mapped by the plaque electrode after the addition of antiarrhythmics.

Interventional study

To evaluate the effect of a linear ablation technique, regional compartmentalization of either the right atrial free wall alone (4 pigs) or together with the left atrial appendage (4 pigs) was performed by epicardial cryothermal linear ablation (Cryo-unit 142, Spembly Medical Corp., Andover, United Kingdom). The cryoablation lesions were applied consecutively by a T-shaped ablation probe at -60 ℃ (for 60 sec each) along the designed compartmentalization lines. For isolation of

the right atrial free wall, ablation lines were connected from the orifice of the superior vena cava to that of the inferior vena cava as well as to the anterolateral aspect of the tricuspid annulus, including the right atrial appendage. If AFib persisted, another ablation line was applied to encircle the orifice of the left atrial appendage. The effectiveness of atrial cryothermal compartmentalization was confirmed by demonstration of independent activation wavefronts in each of the compartmentalized atrial tissue by plaque electrode mapping.

Pathological and histological examinations

At the end of study, the animals were euthanized by high-dose intravenous barbiturate. The atrial pacemaker was removed and the heart was excised and weighed and inspected immediately. All the cryoablation lines were examined grossly and histologically. Tissue blocks from multiple locations including the appendages, the lateral walls, the posterior walls and the septum of both atria were excised for light and electron microscopic examinations.

Data processing and frequency component analysis

Data processing: The intracardiac recordings of bi-atrial plaque mapping were recorded and stored on optical disc using a commercial recording system (Cardiomap™, Prucka Engineering Inc., Houston, Texas). This system used conventional electrocardiographic filtering (0.04 to 100 Hz) and a digital sampling rate of 1024 Hz. Thirty-second recordings from 224 bipoles on the plaque were then analyzed off-line on a microcomputer. Software used to perform the analysis was developed using Matlab programming language (The Mathworks Inc,. Natick, Massachusetts). We divided each 30-second intracardiac recording into 15 segments with 2 seconds per segment. Each two-second intra-atrial recording was subjected to 2048-point discrete Fourier transformation after application of a Hamming window.

Peak frequency: After Fourier transformation, all two-second recordings were

displayed as power spectra. These spectra were quantified by measuring the peak frequency in a frequency range of 4 to 10 Hz (i.e. 240 to 600 bpm). The peak frequency was identified by a method involved two steps. First, all frequencies with maximal power in each hump of frequency band in a power spectrum were identified. Second, all frequencies with power over 50% of the maximal power were taken as the peak frequencies.

Dominant frequency: Dominant frequency was defined as the frequency which emerged the most common in each 30-second recording. We analyzed the dominant frequencies in 224 bipolar electrodes of plaque mapping, before and after propafenone or sotalol administration or cryoablation.

Other frequency domain parameters: They were defined as follows. FmaxA, dominant frequency with the largest amount of bipolar signal recording sites during the 30-second recording; FmaxD, dominant frequency with the longest time of appearance during the 30-second recording; F_{SD}, standard deviation of all dominant frequencies derived from the 224-site recordings, representing the dispersion of frequencies.

Statistics

Paired continuous data were compared by paired student *t* test. Categoric data were compared by Chi-Square 2×2 or N×M test with Yates' correction. A p valve less than 0.06 was considered as statistically significant.

Results

Induction of sustained AFib in adult pigs

Twenty-two (88%) of the 25 pigs in the study group and 3 (100%) of the 3 pigs in the sham group survived 6 weeks after the implantation of atrial pacemaker. Three pigs in the study group died during follow-up period due to pneumonia in one pig,

acute volvulus in one and intractable congestive heart failure in one. The body weight of the survived pigs in the study group increased from 75±14 kg (range 52 to 90 kg) to 100±16 kg (range 80 to 125 kg) in 6 weeks without evidence of fluid retention. The weight gain was similar in the sham group, i.e. from 70±8 kg (range 62 to 80 kg) to 95±9 kg (range 76 to 110 kg).

After discontinuance of atrial pacing, sustained AFib (

20 (91%) of the 22 survived pigs in the study group, but in none of the sham group. AFib was left persistent for 24 hours in 6 pigs, 48 hours in 7 and 72 hours in 7 prior to the electrophysiological mapping. Two pigs in the study group had nonsustained AFib lasting less than 24 hours after termination of pacing.

Transthoracic echocardiography before and after continuous atrial pacing revealed significant increase in the left atrial dimension (26 ± 3 mm vs. 31 ± 4 mm, P = 0.01), but not in the left ventricular end-systolic (29 ± 4 mm vs. 32 ± 6 mm, P = 0.28) and the end-diastolic (49 ± 5 mm vs. 53 ±9 mm, P = 0.26) dimensions, or the left ventricular fractional shortening (40 ± 10% vs. 39 ± 8%, P = 0.77) and the ejection fraction (69 ± 11% vs. 67 ± 10%, P = 0.60).

Bi-atrial epicardial mapping of sustained AFib

All of the 22 survival pigs in the study group had persistant AFib throughout the open-chest epicardial mapping study. The two pigs with nonsustained AFib could be easily induced into persistent AFib by one to three electrical extrastimuli from the right or the left atrium. The mean ventricular rate was 77 ± 3 bpm in the 20 pigs with sustained AFib, and 74 bpm in the other two pigs with paroxysmal AFib.

All of the AFib revealed the coexistence of multiple reentrant wavelets by epicardial mapping. The wavelets propagated, migrated, collided and generated new daughter wavelets. None of the wavelets circulated in a stable pathway. The number of activation wavelets recorded at the left atrial free wall (10.6 ± 2.9 wavelets/cm^2/sec)

was generally higher than that at the right atrial free wall (7.6 ± 2.4 wavelets/cm^2/sec, P < 0.002), as calculated by dynamic analysis of activation sequences. The mean local A-A intervals were 87.2 ± 14.6 msec in the left atrium and 103.3 ± 19.0 msec in the right atrium (P < 0.0002). The mean coefficiency of variance was 7.4 ± 3.9% in the left atrium and 7.9 ± 4.1% in the right atrium (P = 0.77).

Frequency domain analysis of the atrial local signals from 224 bipolar sites of plaque recordings at both right and left atria was listed in Table 1. As shown, the mean of dominant frequency detected during porcine persistent atrial fibrillation was significant higher at left atrium (6.8 ± 0.8 Hz) than at right atrium (6.5 ± 0.5 Hz, p 0.002 vs left atrium). However, the number of dominant frequencies was more at the right atrium (3.6 ± 1.8) than that at the left atrium (2.8 ± 1.5, p 0.016). Dispersion of dominant frequencies was similar between the left and the right atria. The frequency domain manifestation supported the driver role of the left atrium. Whereas, probably due to underlying atrial pathology, the existence of dominant frequency was unexpectedly more common at the right atrium, rather than at the left.

Pharmacological study

Sustained AFib induced in the present model could not be terminated by intravenous dl-sotalol in any of the 6 tested animals. The mean local A-A intervals after dl-sotalol did not change significantly either in the left atrium (102.4 ± 20.3 msec, vs. 89.4 ± 12.6 msec, P= 0.11) or in the right atrium (120.8 ± 29.6 msec, vs. 99.8 ± 13.1 msec before dl-sotalol, P = 0.10). The number of co-existing activation wavelets was similar before and after the use of sotalol (left atrium, 10.7 ± 3.8 vs. 9.3 ± 3.4 wavelets/cm^2/sec, P= 0.21; right atrium, 7.2 ± 2.2 vs. 6.5 ± 3.5 wavelets/cm^2/sec, P = 0.34). Activation wavefronts remained meandering and unpredictable in dynamic display.

From frequency component point of view, sotalol effectively reduced the mean

of dominant frequencies, the dominant frequency with largest electrode area and the dominant frequency with longest appearance time (Table 2). Meanwhile, the frequency dispersion was decreased at the left atrium, and not changed at the right. The number of dominant frequency was decreased at the right atrium, but not the left. Apparently, sotalol as a potassium channel blocking agent was more effective in prolongation of local atrial refractoriness and subsequently the circuit length of reentrant wavelets.

In contrast, intravenous propafenone terminated AFib in 3 of the 5 study animals. All of the acutely terminated AFib could be immediately reinitiated by one to three electrical extrastimuli to the left atrial wall. The mean local A-A intervals after propafenone, measured during sustained AFib in two pigs or reinduced AFib in three, prolonged significantly in the right atrium (143.0±30.5 ms vs. 107.8±16.0 ms, after vs. before propafenone, $P<0.05$), but not in the left atrium (141.3±58.2 ms vs. 96.8±16.2 ms, $P=0.14$). In dynamic display, propafenone apparently reduced the number of reentrant wavelets at both the left atria (4.5±2.0 vs. 10.4±3.2 wavelets/cm^2/sec, after vs. before propafenone, $P<0.05$) and the right (2.1±1.2 vs. 8.0±3.1 wavelets/cm^2/sec, after vs. before propafenone, $P<0.04$). The activation wavelets after propafenone appeared more organized and rotated in a larger radius, although the migratory characteristic of the wavelets remained unchanged.

As to the frequency domain analysis in propafenone intervention (Table 2), we could note that only the dominant frequency at the left atrium was decreased after propafenone, i.e. the mean of dominant frequencies and the dominant frequency with the longest appearance time. None of other frequency characteristics changed after adding propafenone. Neither was the dispersion of dominant frequencies or the number of dominant frequencies in atrial fibrillation. Propafenone had significantly suppressed the sodium channel-dependent portion of the reentrant spiral wave, i.e. the

core of the spiral rotor at the left atrium. However, the lack of propafenone effect at the right atrium was intriguing and might be closely related to the inherent structural obstacles in it.

Atrial compartmentalization by epicardial cryoablation

Despite effective cryo-compartmentalization in the right atrial lateral wall alone (4 pigs) or together with the left atrial lateral wall (4 pigs), sustained AFib did not terminate in any of the 8 animals receiving this interventional proceduce. Direct epicardial recordings confirmed effective compartmentalization of the atrial tissue by demonstration of independent regular activation wavefronts inside the compartments (Figure 4-A). The mean local A-A interval was 285.7 ± 30.4 msec inside the isolated right atrial free wall (8 pigs) and 260.2 ± 28.1 msec inside the isolated left atrial appendage (4 pigs). The atrial wall beyond the cryoablation lines remained in multiple reentrant wavelet activations, with mean local A-A intervals of 105.5 ± 40.5 msec in the spared left atrium after right atrial compartmentalization ($P < 0.02$, vs. the isolated right atrial wall).

Pathological and histological findings

The weight of the excised hearts was 550 ± 14 gms (range 480 to 670 gms) in the study group and 408 ± 10 gm (range 370 to 430 gm, $P<0.03$) in the sham group. Serosanguious pericardial effusion ranging 30 to 120 ml was found in 10 pigs in the study group. None were found to have atrial perforation due to a penetrating atrial lead. The cryoablation lines over the right atrial anterior and posterior walls and the root of the left atrial appendage were all transmural by gross inspection. No atrial thrombus was found.

Discussion

Based on a pig model of persistent atrial fibrillation, the present study demonstrated that the driving frequency of the left atrium was significantly faster than that of the right atrium. The driving frequencies of both left and right atria could be effectively suppressed by potassium channel blocker (sotalol), but not sodium channel blocker (propafenone).

Recent experimental studies in dogs (14, 15) have demonstrated that the density of the rapid delayed rectifier current (IKr) is higher in the left atrium. The ether-a-go-go-related gene protein is also more expressed in the left atrium. Nevertheless, the slow and ultrarapid delayed rectifier, L-type calcium and transient outward potassium current are similar between the right and left atria. The ionic channel heterogeneity apparently leads to the shorter action potential duration of the left atrium and the more decrease of action potential duration to dofetilide (IKr blocking agent) at the left atrium. Our study of porcine atrial fibrillation supported the observations in dogs by showing that the dominant frequency in the left atrium was of higher rate than that in the right. The left atrium was responsive to both sotalol and propafenone and showed the significant decrease of dominant frequencies. In contrast, the right atrium was only responsive to sotalol, but not to propafenone. We could speculate that the activation wavefronts of atrial fibrillation in the left atrium was more potassium channel-related and more reentry in mechanism. So was that in the right atrium. In contrast, the concept of meandering spiral waves or spiral rotor drive was partly discouraged by the less evident response to propafenone in the “driving” left atrium, although not unlikely.

However, both fixed and unstable circuits of reentry are a mixture of anatomical and functional obstacles with variable excitable gaps. The more the functional component, the more response to sodium channel blocker and the more lengthering of

reentrant circuits (16). Apparently, the atrial fibrillation activations in the left atrium resulted from both anatomical and functional mechanisms. Yet, the fibrillation in the right atrium was more anatomically, but not functionally, determined. Taking together the frequency domain characteristics and responses to distinct ion channel blockers, we supported that the left atrium was a driving center for atrial fibrillation and the right atrium was more a passive portion. Nevertheless, the driver in the left atrium was not totally a functionally –determined active spiral rotor. Furthermore, the heterogeneity of anatomical structure including superimposed pathology and inherent functional variations (15, 17) in the right atrium was ironically more evident in the right atrium, but not the expected left one. The contributory mechanisms are unknown (14, 15, 17, 18).

In conclusion, by means of frequency domain analysis, the present study demonstrated that the left atrium was a driving center for persistent atrial fibrillation in our pig model of chronic atrial overdrive pacing. The driving source in the left atrium was most likely a reentry circuit with both anatomical and functional components. Whereas, the fibrillatory activation in the right atrium was heavily determined by complex anatomical structures and much less functional component.

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Table 1. Frequency domain analysis of atrial local electrograms from 224-site bipolar recordings in pigs with persistent atrial fibrillation

	DF#	DF_{disp}	$DF_{max}A$	$DF_{max}D$	DF_{AVG}
LA	2.8 ± 1.5	0.29 ± 0.34	6.7 ± 0.9	6.9 ± 0.8	6.8 ± 0.8
RA	3.6 ± 1.8	0.40 ± 0.37	6.4 ± 0.7	6.5 ± 0.6	6.5 ± 0.5
P	0.016	0.17	0.025	0.000	0.002

DF, dominant frequency, in Hz; DF_{AVG}, mean of dominant frequencies (DF), in Hz; $DF_{max}A$, dominant frequent with largest bipole number or area, in Hz; $DF_{max}D$, dominant frequency with longest duration of appearance, in Hz; DF_{disp}, dispersion of dominant frequencies, i.e. maximal-minimal dominant frequency, in Hz; DF#, number of dominant frequencies; LA, left atrium; RA, right atrium.

Table 2. Influence of antiarrhythmic drugs (propafenone and sotalol) in frequency components of persistent atrial fibrillation in the pig model.

	DF#	DF_{disp}	$DF_{max}A$	$DF_{max}D$	DF_{AVG}
LA					
pre-STL	3.4±1.6	0.39±0.35	6.7±0.7	7.0±0.6	6.9±0.7
post- STL	2.9±1.1	0.20±0.11*	5.8±1.5†	5.8±0.5†	5.8±0.4**
RA					
pre- STL	4.3±2.1	0.38±0.26	6.5±0.5	6.6±0.5	6.4±0.5
post- STL	2.6±1.2**	0.25±0.41	5.3±0.5†	5.4±0.5†	5.4±0.5†
LA					
pre-PPF	2.8±1.2	0.27±0.36	6.7±0.9	6.9±0.7	6.8±0.8
post-PPF	2.8±1.7	0.570±0.90	5.8±1.5	5.9±1.5*	6.0±1.2*
RA					
pre-PPF	3.4±1.4	0.40±0.54	6.8±0.8	6.8±0.8	6.9±0.5
post-PPF	2.9±1.6	0.63±0.91	5.9±1.4	5.9±1.4	6.2±1.2

PPF, propafenone; pre-, post-, before, after the addition of; STL, sotalol; Other abbreviations as in Table 1; *, $p<0.05$; **, $p<0.001$; †, $p<0.0001$.