國家科學委員會專題研究計劃

第三年進度報告

題　　目

利用新型高柔度電氣燒灼導管製造線形心房切割以控制心房顫動之雜種狗研究

Radiofrequency Linear Ablation in the Atria to Control Sustained Atrial Fibrillation in a Canine Model by the Use of A Novel Pliable Electrode Catheter

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主　持　人：　臺大醫學院　臨床醫學研究所

黃水坤　教授

共同主持人：　臺大醫學院　內科

林俊立　副教授

Introduction

The interventional therapy of chronic atrial fibrillation is currently in the dilemma of decision-making in regards of the selection of ablation targets between the arrhythmogenic substrate and the arrhythmic triggers. Either approach may well be rewarding. Open-heart maze procedure (1) and atrial compartmentalization (2, 3) are effective in the restoration of stable sinus rhythm for valvular heart diseases combined with chronic atrial fibrillation and undertaking valvular replacement or reconstruction. On the other hand, transcatheter radiofrequency ablation is also effective in the elimination of certain paroxysmal atrial fibrillation by targeting at the pulmonary vein orifices or vena caval junctions (4, 5). The former "reorganizes" the atrial substrate, while the latter eradicate the responsible atrial triggers. However, limited by contemporary shortage in ablation technologies and relevant knowledge, none of the aforementioned approaches can be reliably and safely conducted by transcatheter radiofrequency application, due to either the difficulty of creation of linear transmural atrial lesions or the unpredictable emergence of neo-triggers from diseased atria.

In the third year of the project, we attempted to identify the source of chronic atrial fibrillation in the established pig mode of atrial fibrillation (5). By both dynamic illumination display and frequency analysis of local atrial electrograms, we demonstrated that both the right and the left atria had simultaneous existence of multiple small activation wavefronts, none with complete re-entry rotations in chronic sustained atrial fibrillation produced in the adult pigs. The wavelets could be modified by various antiarrhythmic drugs and atrial interventions.

Methods

Animal preparation.

Twenty-five adult pigs of Yorshire-Landrace strain weighing 60 to 94 kg were used for the study. The experimental protocol was approved by Institutional Animal Care and Use Committee.

All the animals received high-speed atrial pacemaker (Itrel-II, Medtronics) implantation on the first day of experiment. After 4-6 weeks of continuous atrial pacing at 600 BPM, the pacemaker function was shut off. Over 90% of the animals will develop spontaneous sustained atrial fibrillation lasting over 24 hours, as previously reported.

Electrophysiologic studies.

All the survived animals will receive the open-heart electrophysiology study by epicardial plaque (224 sites, 3.5mm interval) mapping of spontaneous atrial fibrillation. The activation sequence of atrial fibrillation will be analyzed in two methods. First, the activation pattern of atrial fibrillation would be constructed by a commercially available multichannel

analysis system (EMAP, Uniservice, New Zealand). The time of activation of each atrial local electrogram was selected automatically by maximal dv/dt threshold, and later edited manually. Then, the pattern of activation would be displayed by dynamic illuminations on a computer screen. Whenever an activation was registered, the corresponding electrode site was illuminated as initially red, then yellow, green, light blue and finally dark blue. The cinematic display help identify individual activation wavefronts and the activation pattern. The number and tracks of activation wavefronts could be analyzed and quantitated in unit area and unit time. The wavebreaks or collision of wavelets could be repeatedly evaluated by the dynamic display system.

Second, the stored digitized data of the recorded atrial bipolar electrograms could be redigitized for Fast Fourier transform (2048-point) analysis of frequency components. The derived power spectra of the frequency contents of each local atrial signals could be quantified for the peak frequencies and the dominant frequencies. The peak frequency of each power spectrum was selected form the central frequency with the maximal power between 4 to 10 Hz. Dominant frequency was defined as the frequency lasting for 60 seconds in each 5-minute recording.

All the activation details of the produced porcine atrial fibrillation were analyzed in baseline and after the application of antiarrhythmic drugs and atrial compartmentalizations.

Pharmacological and interventional tests.

In six pigs with sustained atrial fibrillation, intravenous dl-sotalol (2 mg/kg) was administered for evaluation of antiarrhythmic effects.

In 5 pigs with sustained atrial fibrillation, atrial compartmentalization was performed over right atrial free wall, as described in the second-year report, and intended to isolate a significant mass of the atria. The influence of the intervention was likewise evaluated by direct plaque recording over the epicardium.

Statistics.

Continuous data was expressed as mean ± SD and compared by unpaired or paired t-test. Categoric data was compared by Chi-Square N×M test. A p value less than 0.05 is considered as statistically significant.

Results

Harvest of chronic sustained atrial fibrillation.

After 4-6 weeks of continuous atrial pacing at 600 BPM, 22 (88%) of the 25 pigs survived. All of the survived pigs could be demonstrated to have persistent atrial fibrillation either spontaneously (20 pigs) or easily induced again by 1-3 atrial extrastimuli (2 pigs).

Dynamic display analysis of sustained atrial fibrillation in the pigs.

The dynamic illumination analysis of atrial fibrillation induced in the pig model revealed diffuse, multiple reentry wavelets over both the right and the left atria. The number of activation wavelets over let atrial free wall was 10.6 ± 2.9 wavelets/cm^2/sec, while the number over right atrial free wall was 7.6 ± 2.4 wavelets/cm^2/sec (left vs. right atrium, $P < 0.002$) (Figure 1, 2). None of the reentry wavelets over either the right or the left atrial free wall could be observed to complete a whole rotation in all the studied animals. The mean A-A interval in the left atrial free wall was 87.2 ± 14.6 msec, while that in the right atrium was 103.3 ± 19.0 msec ($P < 0.0002$, left vs. right atrium). The mean cofficiency of variance over the left atrium was 7.4 ± 3.9%, while that over the right atrium was 7.9 ± 4.1% ($P = 0.77$, left vs. right atria). From the activation mapped by the epicardial plaque electrodes, there was no evidence of a dominant origin or active source for the sustained atrial fibrillation induced in the pig model. Both the right and the left atria possessed multiple coexisting re-entrant wavelets, numbering apparently more than six in either atrium. Furthermore, there was no evidence of macroreentrant circuits, at least judged by the 224-site atrial recording plaque electrodes.

Frequency analysis of the activations in sustained atrial fibrillation.

As shown in Table 1, the power spectra for both the right and the left atrial local electrograms have the characteristics of periodic activations, i.e. the existence of dominant frequencies from the mapped regions. The activation components in sustained atrial fibrillation were not random. Instead, the atrial fibrillation was driven by 5.8 ± 1.9 frequencies over left atrium and 5.3 ± 1.4 frequencies over right atrium. The manifestation of the frequency components was nevertheless similar between the right and the left atria in regards of the frequency with maximal appearance time or maximal area, maximal duration of dominant frequencies, maximal area of dominant frequencies, dispersion of dominant frequency distribution areas or dispersion of dominant frequencies. (Table 1)

The existence of dominant frequencies persisting for a significant duration (≥ 60 seconds) during chronic sustained atrial fibrillation indicated the periodic nature of the chaotic dysrhythmia. However, whether or not the frequency components represented the cycle length of certain reentrant wavelets or circuits and the locations of the dominant wavelets remained unknown. Further correlation between the frequency spectra and the activation patterns of atrial fibrillation would be critical for the search of the possible source(s) in the maintenance of sustained atrial fibrillation in our pig model and human counterparts.

Discussion

By high-density activation sequence analysis in chronic sustained atrial fibrillation of

the pigs, we have found that the electrophysiologic mechanism in chronic atrial fibrillation was multiple, reentrant wavelets, which usually didn't complete a single reentrant circle. In addition, the frequency analysis for the local atrial electrograms from multiple atrial sites revealed a mean of 7-10 dominant frequencies in each atrium. The activation sequences in atrial fibrillation might be complex, but still possessing the characteristics of certain periodic activations.

Source vs. trigger in chronic sustained atrial fibrillation.

Up to the present, the most reproducible success in the elimination of chronic sustained atrial fibrillation in humans remains the open-heart surgery. However, the mechanism underlying the surgical success doesn't seem to be clarified. Both the maze procedure (1) and the atrial compartmentalization (2) reduce the effective atrial mass as well as circumscribe the most vulnerable trigger zone in the atria. Only the left atrial compartmentalization around the convergence area of all four pulmonary veins (3) and the recently-reported circumferential ablation of pulmonary vein orifices (6) may be more fit into the atrial trigger theory. Nevertheless, the latter circumferential ablation by ultrasound balloon had had nearly 30% recurrence in only 3-4 months of observation for a group of mostly paroxysmal atrial fibrillation patients.

The mapping of sustained atrial fibrillation in our pig model indicated the presence of a mean of at least ten dominant frequencies by frequency analysis and more than 15 reentrant wavelets per sec per cm^2 in the two atria. The observations demonstrated the complexity of activation patterns in chronic atrial fibrillation, but also depicted the existence of certain circuit routes in the atria. Further spatial localization or spatio-temporal coordinated analysis may help pave the way for the designing of strategic ablation techniques, although the day of clinical breakthrough stays unknown.

Technological bottleneck in transcatheter ablation of atrial fibrillation.

The center for the maintenance of atrial fibrillation can be well speculated to be wide and probably multiple. The difficulty in identification of the critical site(s) for application of therapeutic energy came from several key questions. First, the creation of transmural lesions for variable geometry in the atria, particularly the pectinate muscle folds; Second, the efficient creation of long and continuous linear or circular lesions in the atria; Third, the decision in selecting the appropriate target zone for atrial fibrillation. Our electrophysiological mechanism study in the chronic pig atrial fibrillation model may bring some answers to the third problem, but not the more engineering-based first and second problem. Actually, without a scapel-like precision technique in ablation, the efficacy of transcatheter approach in the eradication of atrial fibrillation can never be evaluated.

Conclusion

In the third year of the project, we devoted into the research of the electrophysiological and driving mechanisms in chronic sustained atrial fibrillation by means of an established adult pig model. On the other hand, the limitation in ablation devices and/or energy source have certainly precluded the attempt in interventional treatment of chronic atrial fibrillation, at least not as optimistic as in the beginning of the project.

References

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Table 1. **Frequency Characteristics of Local Atrial Activations in Chronic Sustained Atrial Fibrillation**

	Freq. #	F-max A	F-max D	A max	D max	Disp-A	Disp-Freq
Left atrium	5.8±1.9	6.9±0.6	6.8±0.7	23.5±2.7	121.4±3.4	5.7±2.3	0.8±0.2
Right atrium	5.3±1.4	6.3±0.5	6.4±0.6	21.5±7.6	121.6±2.6	5.4±2.0	0.7±0.2

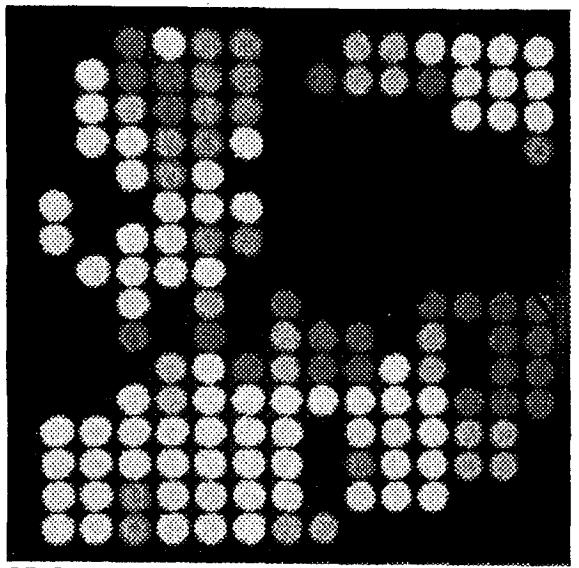
Freq #, number of dominant frequencies; F-max. A (Hz), frequency component with maximal area of distribution; F-max, D (Hz), frequency component with maximal duration; A max (%), maximal area of a dominant frequency occupies; D max, maximal duration (sec) of a dominant frequency; Disp-A, -Freq, coefficiency of variance of distribution area and frequency of dominant frequencies. no difference was found between left and right atrium in any parameter.

Figure Legends

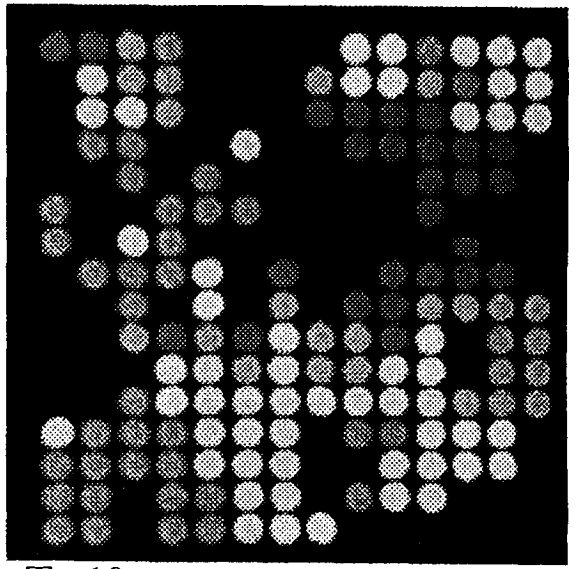
Figure 1. Activation patterns in right atrium during spontaneous atrial fibrillation in a study pig. T 0, 10, 25, 35 ms, time sequence after the onset of dynamic illumination display.

Figure 2. Activation patterns in left atrium during spontaneous atrial fibrillation in the same pig as Figure 1. Abbreviations, as in Figure 1.

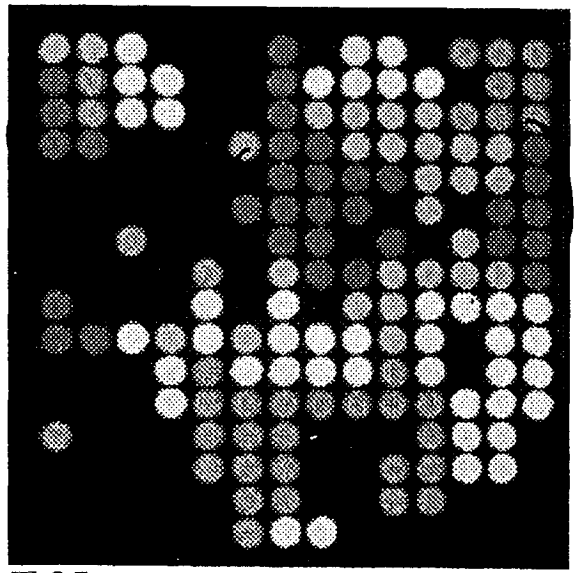
RA activation sequence during AF



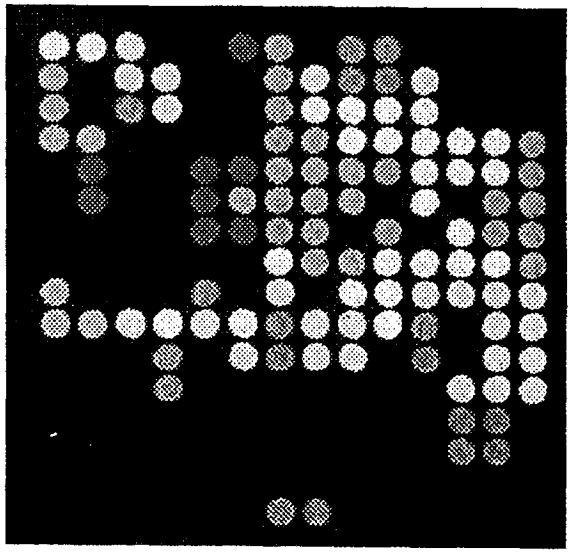
T 0 ms



T 10ms



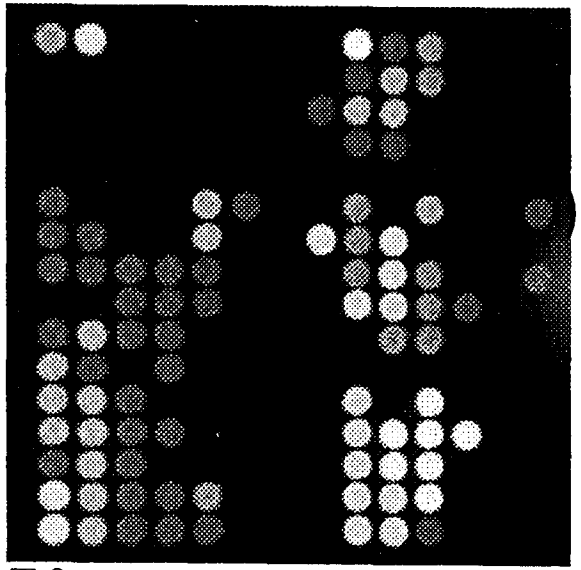
T 25ms



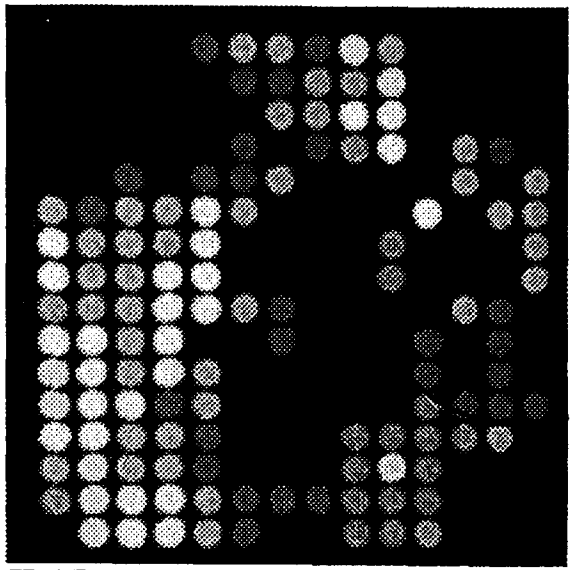
T 35ms

(Figure 1)

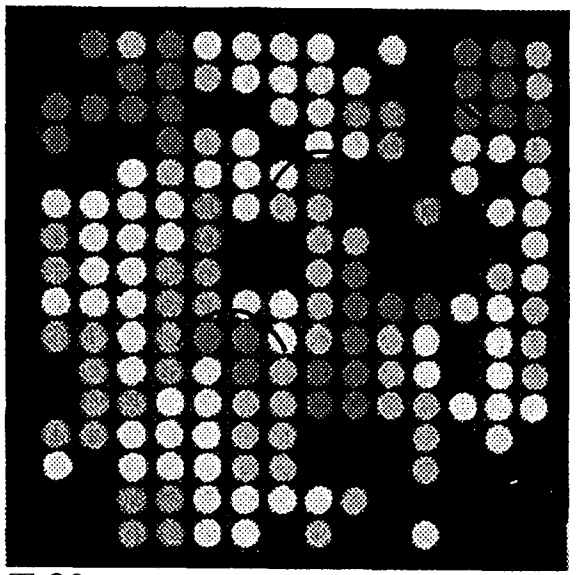
LA activation sequence during AF



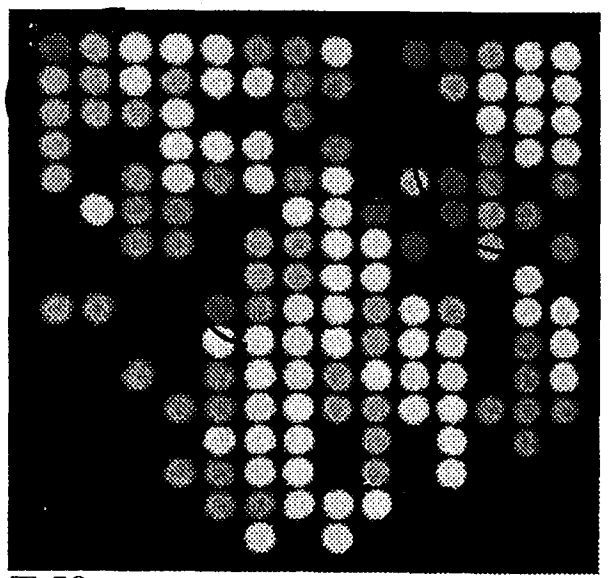
T 0 ms



T 15ms



T 30ms



T 50ms

(Figure 2)