A dual model for cardiac arrhythmias: coexistence of re-entry and abnormal automaticity and effects of antiarrhythmic agents

¹Kuei-Meng Wu, Thomas Hunter & Anthony Proakis

Department of Pharmacology, A. H. Robins Research Laboratories, Richmond, VA 23261, U.S.A.

1 We have developed a dual model for arrhythmia in anaesthetized dogs. The model consists of an inducible re-entrant atrial tachycardia and spontaneous ventricular ectopies in the same heart.

2 The model for re-entrant atrial tachycardia was created by crushing the right atrium longitudinally in the intercaval region and transversely in the front free wall parallel to the atrioventricular groove. Ventricular abnormal automaticity was produced by prior (20 ~ 24 h) left anterior descending coronary artery occlusion. The ventricular arrhythmia was partially suppressed during rapid pacing-induced atrial tachycardia and resumed after atrial re-entry was terminated.

3 Mapping experiments indicate that the atrial tachycardia was due to circus movement occurring in the tissue around the tricuspid ring. This re-entrant circuit was identical to that induced in the model created by the incision method.

4 Clofilium (0.75 mg kg^{-1} , $n = 5$) increased the cycle length of atrial re-entry by $14 \pm 4\%$ from 139 ± 12 to $159 \pm 18 \text{ ms}$ ($P < 0.05$). Flecainide ($1.8 \pm 0.9 \text{ mg kg}^{-1}$, $n = 5$) prolonged the cycle length of the tachycardia by $114 \pm 57\%$ from 158 ± 11 to $332 \pm 66 \text{ ms}$ ($P < 0.05$).

5 Both drugs terminated the atrial arrhythmia, but re-entry could be reinduced only in flecainide-treated dogs. Flecainide reduced ventricular ectopies by $89 \pm 19\%$, whereas clofilium did not change ventricular abnormal automaticity or maximum pacing cycle length that is necessary to overdrive the ventricle fully.

6 These data indicate that the dual model provides coexisting arrhythmias of different mechanisms in the same heart and that Class I and Class III anti-arrhythmic drugs may be differentiated from each other by the distinct patterns of pharmacological activities produced in this test system.

Introduction

Re-entry and abnormal automaticity are two primary mechanisms responsible for the genesis of cardiac arrhythmias (Hoffman & Rosen, 1981). Ventricular arrhythmias in dogs after occlusion of a coronary artery for 20–24 h are believed to be due to abnormal automaticity, which occurs in a *de novo* or triggered fashion, in the endocardial Purkinje fibres of the infarcted zone (Friedman *et al.*, 1973a,b; Lazzara *et al.*, 1973; 1978; El-Sherif *et al.*, 1983). This type of arrhythmia is frequently used to assess the antiarrhythmic potential of new chemical entities. Class I antiarrhythmic agents such as lignocaine, procainamide, quinidine and flecainide have been shown to suppress multifocal ectopies in the 1-day myocardial infarcted dog model. Recently, a conscious model for re-entry arrhythmia in the dog has

been developed (Frame *et al.*, 1986; Wu & Hoffman, 1987). The arrhythmia is a result of re-entrant excitation propagated in a partially repolarized atrial tissue around the tricuspid ring (Frame *et al.*, 1986; 1987; Wu *et al.*, 1989a). The circus movement is easy to induce, stable in cycle length, and persistent. Various antiarrhythmic agents have been studied in this model of arrhythmia (Wu & Hoffman, 1986; Frame & Colatsky, 1987; Spinelli & Hoffman, 1987; Wu & Hoffman, 1987).

It was our objective to combine the model for ventricular abnormal automaticity due to prior (20 ~ 24 h) coronary artery occlusion and the model for re-entrant atrial tachycardia in the same canine heart. In addition, we used the sodium channel blocker, flecainide, and the potassium channel blocker, clofilium, to examine the antiarrhythmic patterns of these agents in this dual model for arrhythmia.

¹ Author for correspondence.

Methods

Dogs of either sex weighing 10–16 kg were fasted overnight, anaesthetized with pentobarbitone (35 mg kg^{-1} , i.v.), and ventilated artificially. The left side of the chest was opened at the fifth intercostal space and a segment of 0.5–1.0 cm of left anterior descending (LAD) coronary artery proximal to the first diagonal branch was dissected free and occluded by an Ameroid plastic constrictor, according to the method described by Smith *et al.* (1973). Twenty to 24 h after each dog had recovered from the surgery, the animal was reanaesthetized by slow infusion of pentobarbitone (30 mg kg^{-1} , i.v.) and artificially ventilated with its temperature maintained at $37 \pm 0.5^\circ\text{C}$ by a heating pad. The chest was opened at the right side through the fourth intercostal space. The intercaval tissue, extending longitudinally for 5 to 7 cm, was crushed by hemostat clamps. Continuous crushes of 5 to 7 cm long were also performed at the front right atrium branched from the intercaval crushes toward the atrial appendage and in parallel to the atrioventricular groove. Two or 3 pairs of bipolar electrodes were sewn on the posterior wall of the right atrial appendage near the aortic root and Bachmann's bundle for stimulation and recording of local atrial electrograms. For mapping of the activation sequence during stable and regular re-entrant tachycardia, a bipolar roving probe (4 mm in diameter and 10 cm in length) was used for the recording of the epicardial and endocardial electrograms. The roving probe was inserted into the right atrium through a purse string aperture at the tip of appendage to perform endocardial mapping. The location of the recording site was guided and verified by probing with an index finger on the epicardium.

Lead II electrocardiogram (ECG) and local atrial electrograms were displayed and recorded on a Electronics for Medicine (Model DR-8) recorder and Grass polygraph (Model 7). Electrical stimulation of the atrium was provided by a digital stimulator and constant current stimulation isolation unit (Model DTU-201, Bloom Associates). The effective refractory period of the right atrium (AERP) was measured at a paced cycle length of 300 ms. A series of 8 impulses (S1), 1 ms in duration and 2 times the diastolic threshold, followed by a premature stimulus (S2) of the same strength was delivered through a bipolar electrode. The S1–S2 intervals were decreased progressively by 5 or 10 ms. The AERP was defined as the shortest S1–S2 interval that produced a propagated response. Re-entrant atrial tachycardia was induced by rapid pacing of the right atrium with a roving bipolar electrode connected to a Grass stimulator and a stimulation isolation unit (Model S48, 2 ms pulse width, 4–8 volts, 100 to 120 ms cycle length). Conduction velocity (m s^{-1}) of

the induced atrial tachycardia was estimated by dividing post mortem tricuspid ring circumference by the cycle length of the atrial re-entry.

Ventricular arrhythmias in postinfarcted dogs were quantitated as % ectopies of total resting rhythm over a period of 10–20 s. Ventricular ectopic beats were identified by the abnormal R waves of the ECG in which the preceding local atrial electrograms do not occur at normal P–R intervals before the QRS complexes. The maximum pacing cycle length (MPCL) that produced 100% suppression of the ventricular ectopies was obtained by pacing at the right atrium beginning at 250 ms and increased at intervals of 50 ms. The presence of the overdrive suppression of ventricular abnormal automaticity was determined by atrial pacing at 250 ms cycle length and expressed as intervals from the last paced QRS complex to the first spontaneous QRS complex derived from an ectopic focus. In 3 experiments involving flecainide, the right vagal nerve was dissected free in the cervical region and electrically stimulated with a Grass stimulator to inhibit atrial overdrive, thereby revealing residual ventricular abnormal automaticities during resting rhythm before and after drug administration.

Heart rate, MPCL, AERP, and % ventricular ectopies were measured before and after intravenous infusion of clofilium tosylate or flecainide acetate with a Harvard infusion pump. The infusion rate of clofilium and flecainide was 0.25 and $0.2 \text{ mg kg}^{-1} \text{ min}^{-1}$, respectively. The infusion of clofilium was continued for 3 min in all trials (0.75 mg kg^{-1}), whereas flecainide was given until atrial re-entry was terminated or a total of 1.6 mg kg^{-1} was delivered. AERP was determined at the end of infusion followed by pacing and other measurements. All post-drug measurements were completed at 5–15 min after drug administration. Changes in the cycle length of the atrial tachycardia were also recorded during drug administration. Data are expressed as the mean $\pm$ standard deviation (s.d.) and differences between treatment groups were analyzed by Student's *t* test with significance level chosen at $P < 0.05$. A paired *t* test was also used for comparisons between predrug controls and postdrug effects within the same treatment group. Clofilium tosylate and flecainide acetate were kindly supplied by Eli Lilly and Riker Laboratories, respectively. Doses are expressed as the salt form of the compounds.

Results

One day following LAD coronary artery occlusion, the incidence of ventricular ectopic activity was $77 \pm 25\%$ at an average heart rate of 174 ± 24 beats

per min ($n = 10$) under open-chest and anaesthetized conditions. The MPCL required to overdrive fully ventricular arrhythmia was 280 ± 35 ms. Overdrive suppression was 387 ± 77 ms following atrial pacing at a cycle length of 250 ms. The first returning spontaneous beat following 250 ms atrial pacing was always ectopic. Atrial re-entry induced by rapid pacing showed stable and regular cycle lengths of 151 ± 12 ms ($n = 10$). During atrial tachycardia, ventricular ectopic activities were partially suppressed (see Figures 2b and 3b) but resumed after atrial circus movement was terminated by rapid pacing. Because we employed crushes instead of incisions as the method for preparing the re-entry model, we confirmed that the current model had the same pathway for circus movement as that created by the incision method. For this purpose, we performed Mines' tests (Mines 1913; 1914) for re-entry by applying tension around the tricuspid ring on either the left or right side of the AV groove with a ligature. The atrial tachycardia was first slowed down and then terminated in all trials. We also conducted mapping experiments in 3 dogs by using a roving probe to record local activation sequence on the epicardium and endocardium of the right atrium. Figure 1 depicts a right atrial isochrone map characterizing a single episode of a counterclockwise re-entrant tachycardia. The right atrial endocardium was displayed two-dimensionally, in a similar way to that described by Frame *et al.* (1987), by cutting open the intercaval region on the left side and from the tip of the appendage towards the superior vena cava and aortic root. The activation times at each epicardial and endocardial site were sequenced in relation to a fixed electrode. Note that bridging of the activation sequence in the whole tachycardia cycle occurred around the tissue of the tricuspid ring. Also, the circulating impulses spread away from the tricuspid ring tissue toward the surrounding portion of the atrium. This circuit path for re-entry is identical to that induced in the model created by the incision method (Frame *et al.*, 1986; 1987).

Clofilium, at the infusion dose of $0.75 \text{ mg kg}^{-1} 3 \text{ min}^{-1}$, significantly prolonged cycle length (Table 1) and terminated the atrial arrhythmia in all dogs. In all cases, neither rapid pacing nor premature stimulation could reinitiate the re-entrant tachycardia. AERP showed significant increases that were greater than the degree of cycle length prolongation (Table 1). Conduction velocity, estimated from tachycardia cycle length and the tricuspid ring circumference, showed decreases that are comparable to cycle length changes (Table 1). Clofilium increased ventricular ectopies in 2 of 5 dogs. In the remaining 3 dogs, the ectopic frequency in the presence of clofilium did not deviate by more than 10%. Following clofilium, heart rate during resting rhythm was

Figure 1 Isochrone map of the two-dimensional right atrium during a counterclockwise re-entrant atrial tachycardia (indicated by the open arrows). Thin lines are isochrones labelled with activation times (in ms) at 10 ms intervals; (●) and (○) represent recording sites on the epicardium and endocardium, respectively. Shading indicates crushed area. Solid arrows on the left and right margins link the continuous portion of the tissue, i.e., intercaval tissue and appendage, that was cut apart for display. Shaded arrows on the top and bottom margins indicate continuous wavefronts propagated from the opposite wall of the atrial appendage.

increased in 1 dog and decreased in 4 dogs. MPCL, which was needed to overdrive the ventricle, was not significantly changed by clofilium (Table 1). Figure 2 is representative of the effect of clofilium on this dual model for arrhythmia. In Figure 2a, over two-thirds of the rhythm showed dissociation of ventricular and atrial activities with the first, second, and ninth as sinus beats. Panel (b) displays the rhythm during re-entrant atrial tachycardia at a cycle length of 145 ms with a 3:2 A-V ratio. Panel (c) shows that clofilium prolonged atrial re-entry to a cycle length of 158 ms. Ten seconds later the tachycardia was terminated. Panel (d) is the resting rhythm indicating that ventricular arrhythmia was not corrected after administration of clofilium.

At average doses of $1.8 \pm 0.9 \text{ mg kg}^{-1}$, flecainide prolonged atrial tachycardia cycle length (Table 1) and terminated the re-entry in all cases. The doses of flecainide that were required for the termination of re-entry were more variable than clofilium (ranged from 0.64 to 1.6 mg kg^{-1}). In those dogs in which the termination of arrhythmia occurred before the 8th

Table 1 Effects of clofilium and flecainide in a dual model for arrhythmia in the dog

Parameter	Control (n = 5)	Clofilium (n = 5)	Control (n = 5)	Flecainide (n = 5)
Heart rate (bpm)	187 ± 26	148 ± 22	161 ± 15	153 ± 16
% ectopy	78 ± 28	89 ± 15	76 ± 25	9 ± 13*†
% change (ectopy)		14 ± 24		-89 ± 19
MPCL (ms)	280 ± 27	290 ± 22		
ARCL (ms)	139 ± 12	159 ± 18*	158 ± 11	332 ± 66*†
% change ARCL		14 ± 4		114 ± 57†
CV (ms ⁻¹)	0.64 ± 0.06	0.56 ± 0.06*	0.58 ± 0.06	0.29 ± 0.08*
% change (CV)		-12 ± 3		-50 ± 12*†
AERP (ms)	121 ± 13	158 ± 22*	118 ± 13	141 ± 15†
% change (AERP)		31 ± 12*		20 ± 4
Reinitiated ARCL after termination		Not reinducible		193 ± 12

Values are mean ± s.d.

* Significant difference ($P < 0.05$) between treatment and control.

† Significant difference ($P < 0.05$) between clofilium and flecainide.

* Significant difference ($P < 0.05$) as compared with % change ARCL of clofilium group.

ARCL = cycle length of atrial re-entry; CV = conduction velocity;

MPCL = maximum pacing length cycle; AERP = effective refractory period of the right atrium.

minute, flecainide was infused until 1.6 mg kg^{-1} had been given. Note that the magnitude of cycle length prolongation by flecainide was significantly greater than that produced by clofilium (Table 1). The final cycle, in most instances, was usually drastically lengthened before termination of re-entry. Atrial re-entry could always be reinitiated after its termination

by flecainide. However the reinitiated rhythm had a cycle length that was shorter than the maximum cycle length achieved before termination by flecainide. The slowing of conduction velocity was greater than the extent of AERP prolongation (Table 1). Following flecainide, ventricular abnormal beats were fully ablated in 3 dogs and reduced by more than 70% in other 2 dogs. Flecainide did not significantly alter resting heart rate in these dogs. Vagal stimulation in 3 dogs revealed ventricular ectopies with an average cycle length of $431 \pm 64 \text{ ms}$. This cycle length was significantly ($P < 0.05$) longer than that obtained during the control period ($309 \pm 89 \text{ ms}$). Figure 3 is representative of the effects of flecainide on this dual model for arrhythmia. During the control period, ectopic activities in resting rhythm (Figure 3a) were partially overdrive suppressed during atrial re-entry at a cycle length of 145 ms (panel b). During flecainide administration, the atrial re-entry slowed down to a cycle length of 274 ms without any ventricular ectopies (panel c). The tachycardia was terminated about 1 min later and the ectopic rhythm was fully corrected to a sinus rhythm (panel d).

Figure 2 Effects of clofilium on the dual model for arrhythmia: (a) and (b) are predrug control; (c) and (d) are postdrug effects. Panels (b) and (c) show rhythms of re-entrant atrial tachycardia. AEG: atrial electrograms (see text for discussion).

Discussion

We have demonstrated that a re-entrant atrial tachycardia can be induced in 1-day myocardial infarcted dogs. Although tissue crushing instead of the incision method was used to accomplish the injury, the circuit for re-entrant excitation appears identical to the ones reported for the incision method (Frame *et*

Figure 3 Effects of flecainide on the dual model for arrhythmia: (a) and (b) are control, (c) and (d) are effects of flecainide. Re-entrant atrial tachycardia is shown in (b) and (c). AEG: atrial electrograms (see text for discussion).

al., 1986; 1987). Mines' tests for re-entry are satisfied in that (1) block of the circulating impulse by tension upon the pathway terminated the re-entry and (2) continuous activation during a cycle was identified and confirmed in the tricuspid ring by roving probe mapping. Thus, for acute studies, the tissue crushing procedure is simpler and less traumatic than the incision method because it eliminates the tedious suturing required to achieve complete atrial closure or to minimize bleeding and reduces the large traumatized area produced by the clamping of tissue before the cut.

Despite the fact that the models for re-entrant atrial tachycardia and the 24 h post infarction ventricular arrhythmias have been characterized under separate conditions, experimental benefits can be derived by the use of this dual model which provides two contrasting arrhythmias in the same heart. This model offers an obvious economic advantage for the evaluation of the antiarrhythmic efficacy and mechanism of action of new agents since the pharmacological profile can be achieved with half the number of animals. The dual model also provides the opportunity to evaluate not only the specificity of a drug against either type of arrhythmia, but also can be useful in determining the sensitivity of a drug for each type of arrhythmia. Although separate arrhythmia

models could be used for such experiments there is always the problem of interanimal variability. The scientific advantage of this dual model is that the antiarrhythmic action of a drug against either arrhythmia can be analyzed under the same pharmacodynamic and pharmacokinetic conditions. From a clinical standpoint, patients with acute ventricular myocardial infarction may concurrently exhibit re-entrant atrial flutter (Jewitt *et al.*, 1967; Pasternak *et al.*, 1988). The latter often intensifies haemodynamic deterioration. The dual model provides an experimental facsimile of the clinical conditions and could prove useful in determining optimal therapeutic remedies for this cardiovascular problem.

In the present study, clofilium did not produce any significant decrease in ventricular ectopic frequency. Clofilium also failed to reduce the incidence of premature ventricular complex in patients with a history of ventricular arrhythmias (Platia & Reid, 1984). Further, it is known that phase 4 depolarization of normal automatic canine Purkinje fibres is not altered by clofilium (Steinberg *et al.*, 1981). In contrast to its lack of effect on automatic rhythm, clofilium is effective against re-entry. The latter action is presumably due to its effect on delaying repolarization and thus prolonging refractoriness

(Steinberg & Molloy, 1979). Since clofilium has no effect on upstroke velocity of the propagating impulse, it should produce little changes in conduction velocity (Steinberg *et al.*, 1981; 1984). However, during circus movement while the action potential was gradually prolonged by clofilium, takeoff potential of the next impulse shifted to a more depolarized level of membrane potential. This may indirectly cause a reduction in upstroke velocity and a slowing in the conduction of the circulating impulse, as shown by the fact that the cycle length of re-entry was prolonged by clofilium.

Termination of the circus movement should occur when repolarization has been delayed and refractoriness of the tissue increased to an extent that the wavefront of the next impulse is blocked. In the present study, we have observed significant increases in refractory periods that exceeded maximum cycle length achieved after clofilium. These data apparently account for the termination of tachycardia and support the above explanation for the action of clofilium.

In contrast to clofilium, flecainide significantly reduced ventricular ectopies in our model for arrhythmia. This is in agreement with previous studies that have shown flecainide to be very effective in ablating canine arrhythmias induced by ouabain and coronary artery ligation (Kvam *et al.*, 1984). In the re-entry portion of the dual model, flecainide was also effective in terminating the atrial tachycardia. Flecainide depresses phase 0 upstroke and produces a marked slowing in conduction (Kvam *et al.*, 1984) as reflected by the drastic increases in re-entrant cycle length observed in the present studies. Recently, we have also shown that flecainide produces a longer cycle length than clofil-

ium in the same atrial re-entry model in conscious dog (Wu *et al.*, 1989b). The termination of re-entry by flecainide should occur when the excitability of the tissues is insufficiently recovered for impulse propagation. The fact that flecainide increases the refractory period has been reported in human (Vikomo & Ohm, 1982) and canine atrium (Hodess *et al.*, 1979). However, in the present study, the ERP was not prolonged to the extent of the cycle length that was achieved after flecainide. Our results, thus, do not appear to support the above reasoning for the action of flecainide on re-entry termination. The exact mechanisms responsible for the above phenomena warrant further investigation.

To summarize, the pharmacological profiles showed that clofilium was active against re-entry but not abnormal automaticity, while flecainide was active in both types of arrhythmias and produced a longer cycle length than clofilium on re-entry termination.

In conclusion, we have shown that re-entrant atrial tachycardia can be induced in 1-day infarcted dogs that have spontaneous ventricular ectopic activities. While it is evident that other antiarrhythmic agents need to be evaluated in this dual model to realize fully its predictive utility, the sodium channel blocker, flecainide, and the potassium channel blocker, clofilium, could be differentiated from each other based upon their distinctive patterns of activities. Since 2 primary types of arrhythmias can be induced in the same heart, the dual model may provide an excellent tool to evaluate Class I and III antiarrhythmic agents.

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