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ORIGINAL ARTICLE

Effect of Flecainide and Ibutilide Alone and in Combination to Terminate and Prevent Recurrence of Atrial Fibrillation

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BACKGROUND: There is a need for improved approaches to rhythm control therapy of atrial fibrillation (AF).

METHODS: The effectiveness of flecainide (1.5 μmol/L) and ibutilide (20 nmol/L), alone and in combination, to cardiovert and prevent AF recurrence was studied in canine-isolated coronary–perfused right atrioventricular preparations. We also examined the safety of the combination of flecainide (1.5 μmol/L) and ibutilide (50 nmol/L) using canine left ventricular wedge preparations.

RESULTS: Sustained AF (>1 hour) was inducible in 100%, 60%, 20%, and 0% of atria in the presence of acetylcholine alone, acetylcholine+ibutilide, acetylcholine+flecainide, and acetylcholine+ibutilide+flecainide, respectively. When used alone, flecainide and ibutilide cardioverted sustained AF in 40% and 20% of atria, respectively, but in 100% of atria when used in combination. Ibutilide prolonged atrial and ventricular effective refractory period by 15% and 8%, respectively, at a cycle length of 500 ms ($P<0.05$ for both). Flecainide increased the effective refractory period in atria by 27% ($P<0.01$) but by only 2% in the ventricles. The combination of the 2 drugs lengthened the effective refractory period by 42% in atria ($P<0.01$) but by only 7% ($P<0.05$) in the ventricles. In left ventricular wedges, ibutilide prolonged QT and T_{peak}-T_{end} intervals by 25 and 55%, respectively ($P<0.05$ for both; cycle length, 2000 ms). The addition of flecainide (1.5 μmol/L) partially reversed these effects ($P<0.05$ for both parameters versus ibutilide alone). Torsades de Pointes score was relatively high with ibutilide alone and low with the drug combination.

CONCLUSIONS: In our experimental model, a combination of flecainide and ibutilide significantly improves cardioversion and prevents the recurrence of AF compared with monotherapies with little to no risk for the development of long-QT–mediated ventricular proarrhythmia.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: atrial fibrillation ■ electrophysiology ■ flecainide ■ ibutilide ■ pharmacology

There is a need for improved approaches to rhythm control therapy of atrial fibrillation (AF). Here, we examine the efficacy and safety of a combination of 2 commonly used antiarrhythmics. Flecainide and ibutilide are antiarrhythmic drugs that belong to class I and class III, respectively.[1,2] They are commonly used for cardioversion and prevention of AF.[1–4] Their efficacy to acutely cardiovert paroxysmal AF ranges between 30% and 50% compared with placebo.[1,4] A critical side effect of ibutilide is the risk for the development of acquired long QT and related ventricular proarrhythmia (ie, Torsades de Pointes [TdP]).[2] Previous studies have shown that such risk can be reduced or eliminated by concomitant inhibition of the late component of the sodium channel current

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WHAT IS KNOWN?

- The efficacy of flecainide and ibutilide to acutely cardiovert paroxysmal atrial fibrillation ranges between 30% and 50% compared with placebo, and the use of ibutilide is associated with a significant risk of Torsades de Pointes.

WHAT THE STUDY ADDS

- Our experimental study indicates that a combination of flecainide and ibutilide may significantly improve cardioversion of atrial fibrillation compared with monotherapies with little to no risk for the development of Torsades de Pointes.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
APD	action potential duration
CL	cycle length
ERP	effective refractory period
LV	left ventricle
PRR	postrepolarization refractoriness
RA	right atrium
TdP	Torsades de Pointes

(late I_{Na}).[5,6] Flecainide has also been shown to inhibit late I_{Na}.[7] The principal aim of the study was to investigate the effects of flecainide and ibutilide, alone and in combination, on atrial and ventricular electrophysiological parameters and their effects to prevent the induction of AF and the ability to terminate AF in canine-isolated coronary–perfused cardiac preparations. A secondary aim was to assess the safety of the drug combination with respect to the development of long-QT–mediated TdP in canine left ventricular (LV) preparations.

METHODS

This investigation conforms with the Guide for Care and Use of Laboratory Animals. Hearts from 25 purpose-bred adult male Beagle dogs (10–16 kg) were obtained from Envigo (Denver, PA). Dogs were sedated using ketamine (10 mg/kg, IM) and xylazine 2 (mg/kg, IM) and euthanized using euthasol solution (pentobarbital sodium and phenytoin sodium; 0.22 mL/kg, IV). Heparin (human pharmaceutical grade, 1000 U/kg, IV) was administered 3 to 4 minutes before isolation of the heart via a left thoracotomy. Retrograde aortic perfusion of the hearts with ice-cold cardioplegic solution (modified Krebs-Henseleit solution; 16-mmol/L KCl) was immediately performed to rinse the coronary vasculature of blood. The hearts were then placed in a sealed container containing ice-cold cardioplegic solution and transported to our institution via a private courier in an insulated package surrounded by icepacks.

Arterially Perfused Canine Right Atrium With a Rim of Right Ventricle

The entire right atrium (RA) with a thin rim of right ventricular tissue (1–1.5 cm) was dissected from the isolated dog heart, and the preparation was unfolded. The ostium of the right coronary artery was cannulated with polyethylene tubing, and the preparation was perfused with cold Tyrode solution (8 °C) containing 8 mmol/L $[K^+]_o$. Ventricular right coronary branches and the cut atrial branches were ligated using silk thread. The preparation was placed in a temperature-controlled bath (8×6×3 cm) and perfused with Tyrode solution (in mM): NaCl, 129; KCl, 4; NaH_2PO_4, 0.9; $NaHCO_3$, 20; $CaCl_2$, 1.8; $MgSO_4$, 0.5; and D-glucose, 5.5 buffered with 95% O_2 and 5% CO_2 (37.0 °C±0.5 °C).

Arterially Perfused Canine LV Wedge

Transmural wedges with dimensions of ≈3×1.5×1.5 cm were dissected from the anterior-apical aspects of the LV. The tissues were cannulated and perfused with a cold (8 °C) cardioplegic solution. The preparations were then placed in a temperature-controlled tissue bath and perfused with a modified Krebs-Henseleit solution bubbled with 95% O_2 and 5% CO_2 and warmed to 37 °C. The composition of Krebs-Henseleit was (in mM) 118 NaCl, 4 KCl, 2 $CaCl_2$, 1.2 $MgSO_4$, 24 $NaHCO_3$, 1.2 NaH_2PO_4, 2 Na pyruvate, and 10 D-glucose. In all cardiac preparations, the perfusate was delivered to the artery by a roller pump (Master/Flex L/S; Cole Parmer Instrument Co, Niles, IL) at constant pressure (40–50 mm Hg).

Transmembrane action potential recordings were obtained using the floating microelectrode technique (10–25-MΩ DC microelectrode resistance) connected to a high-input-impedance intracellular amplifier (World Precision Instruments, Sarasota, FL). The signals were further amplified and digitized (sampling rate, 2 kHz) using the Spike2 acquisition system (Cambridge Electronic Design, Cambridge, United Kingdom). An ECG (pseudo-ECG) was recorded using 2 electrodes consisting of AgCl half cells placed in the bath solution 1.0 to 1.5 cm from the opposite ends of the atrial and ventricular preparations. The effective refractory period (ERP) was measured by delivering premature stimuli after every 10th basic beat at a pacing cycle length (CL) of 500 ms. The diastolic threshold of excitation, a surrogate of excitability, was determined by increasing stimulus intensity in 0.01-mA steps starting from 0.1 mA, until a steady 1:1 stimulation-activation was achieved. Postrepolarization refractoriness (PRR) was recognized when ERP exceeded action potential duration at the level of 90% repolarization (APD_{90}) in the ventricle and APD_{70} in the atria. Ventricular ERP coincides with APD_{90}, whereas atrial ERP generally coincides with APD_{70}. An acetylcholine (0.5 µmol/L)-mediated AF model was used in the present study. AF

was induced by either delivering a single premature electrical stimulation or by rapid pacing (CL, 80–50 ms for 2–5 s).

Experimental Protocols

Coronary-perfused atrial and ventricular preparations were equilibrated in the tissue bath until electrically stable (30–60 minutes). Three series of experiments were performed. In the first series, conducted in arterially perfused canine RA preparations with a rim of RV, we determined the effect of flecainide (1.5 μmol/L) and ibutilide (20 nmol/L) alone and in combination on atrial and ventricular APD, ERP, PRR, and diastolic threshold of excitation (at a pacing CL of 500 ms). Following the measurement of these parameters, we studied the effect of flecainide (1.5 μmol/L) and ibutilide (20 nmol/L) alone or combined to prevent the induction of acetylcholine-mediated AF. These concentrations of flecainide and ibutilide are within the therapeutic range of plasma concentrations of these agents in the clinic. In a second experimental series, we examined the effect of flecainide (1.5 μmol/L) and ibutilide (20 nmol/L) alone and in combination to terminate nonself-terminating AF. Following the induction of AF, the arrhythmia was allowed to persist for at least 5 minutes before the drugs were introduced. It is noteworthy that in the isolated coronary-perfused RA model of acetylcholine-mediated AF, if AF continues for >1 minute, the arrhythmia will not terminate spontaneously for >1 hour.[8,9] If acetylcholine-mediated AF continued for 45 minutes in the presence of the antiarrhythmic drug(s), this is considered a drug failure for stopping/termination of AF. In cases in which the drug(s) terminated AF within 45 minutes, attempts were made to reinduce the arrhythmia with premature electrical stimulation and rapid pacing for 30 minutes. In a third experimental series, the risk of long-QT and related proarrhythmia was assessed in the presence of ibutilide alone or in combination with flecainide using LV wedge preparations. The TdP score method as previously described by Liu et al[10] was used to estimate the risk of TdP arrhythmias. This method, confirmed by blindly comparing 13 agents with various degrees of probability to cause TdP,[10] incorporates the prime risk factors for drug-induced TdP, such as QT and T_{peak}-T_{End} interval prolongation (measured in the current study). The third experimental series was performed using 3-mmol/L KCl Tyrode solution and at a CL of 2000 ms to sensitize the preparation to the development of long QT and TdP. We also used a higher concentration of ibutilide in this series (50 nmol/L) to enhance the proarrhythmic potential of the drug under study. Action potential recordings were obtained from the midmyocardial cell and epicardial regions of the LV wedges.

Drugs

Flecainide and ibutilide were provided by InCarda Therapeutics, Inc; acetylcholine was purchased from Sigma-Aldrich, St. Louis, MO. Acetylcholine and flecainide were dissolved in distilled water as a 10-mmol/L stock solution. Ibutilide was diluted in 100% DMSO as a 1-mmol/L stock solution.

Statistical Analysis

Statistical analysis of the data was performed using 1-way repeated measures ANOVA or Student *t* test, as appropriate. Data are reported as mean±SD. An SD of <0.05 was considered a significant difference.

RESULTS

Experimental Series I (RA Preparations With a Rim of RV)

Flecainide (1.5 μmol/L) slightly abbreviated APD in both atria and ventricles (n.s.), whereas ibutilide (20 nmol/L) significantly prolonged APD in both atria and ventricles (Figures 1 and 2). The combination of these agents also significantly prolonged APD in both atria and ventricles (Figures 1 and 2). Flecainide alone caused an atrial selective prolongation of ERP secondary to the atrial-selective development of PRR (Figure 2). Ibutilide alone prolonged ERP in both atria and ventricles, secondary to APD prolongation in both atria and ventricles (Figure 2). The combination of flecainide and ibutilide produced an atrial-predominant prolongation of ERP, largely due to atrial predominant induction of PRR (Figure 2). The drug combination caused a greater ERP prolongation in the atrium than either drug alone (Figure 2). Flecainide alone induced an atrial selective depression of excitability (ie, an increase in the diastolic threshold of excitation); ibutilide alone did not affect excitability in either atria or ventricles (Figure 3). The drug combination produced a significant increase in the diastolic threshold of excitation in the atrium but not in the ventricle (Figure 3).

Following the measurement of the electrophysiological parameters in the presence of each drug and the drug combination, we investigated their effect to prevent the induction of acetylcholine-mediated AF. Under control conditions, acetylcholine (0.5 μmol/L) alone sharply abbreviated atrial ERP (from 149±10 to 46±5 ms; $P<0.001$; n=10), permitting induction of AF in 100% of the preparations. Nonself-terminating AF (>1 hour) was inducible in 100% of control preparations, and its appearance was always preceded by the induction of short episodes of AF (lasting <15 s; Figures 4 and 5). Nonself-terminating acetylcholine-mediated AF was inducible in 60%, 20%, and 0% of preparations pretreated with ibutilide, flecainide, and their combination, respectively (Figure 4). Brief episodes of self-terminating acetylcholine-mediated AF and atrial tachycardia (lasting

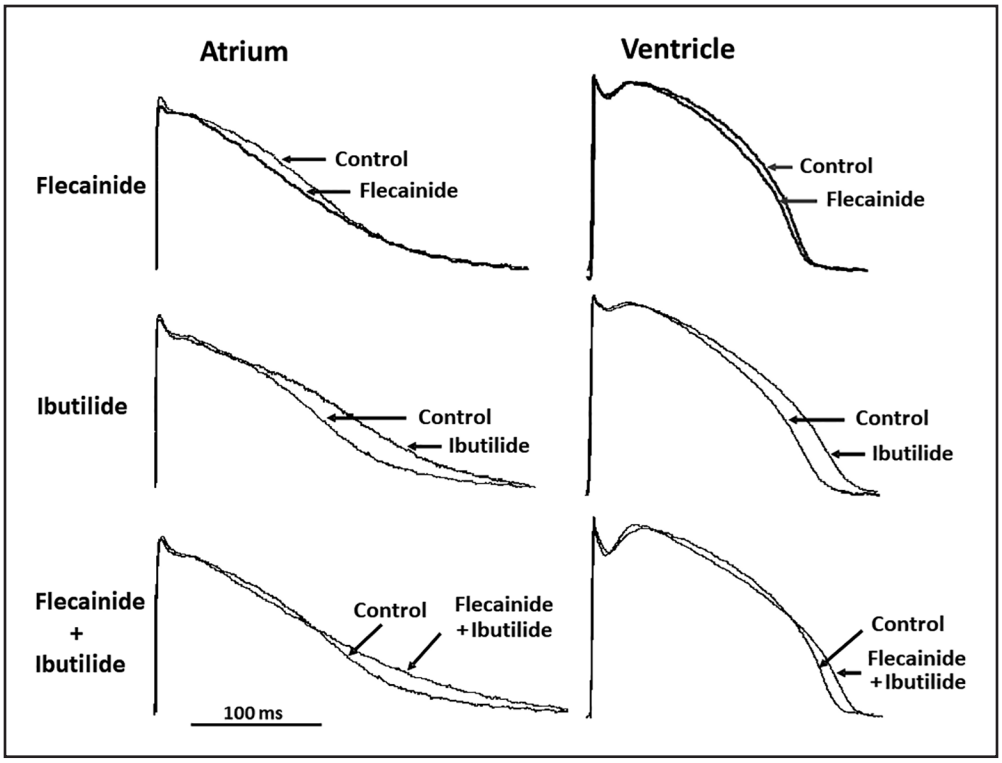

Figure 1. Effect of flecainide (1.5 µmol/L) and ibutilide (20 nmol/L) alone and in combination on atrial and ventricular action potential waveforms.
Cycle length, 500 ms. The data were obtained from right atrial preparations with a rim of the right ventricle.

<10 s) remained inducible with each drug individually (in 80%–100% of the preparations) and with their combination (in 60% of preparations; Figure 4).

Experimental Series II (RA Preparations With a Rim of RV)

In this series, we tested the efficacy of flecainide (1.5 µmol/L) and ibutilide (20 nmol/L), alone and in combination to cardiovert nonself-terminating acetylcholine-mediated AF. Flecainide and ibutilide terminated AF in 40% and 20% atria, respectively, when used alone and in 100% atria when used in combination (Figure 4). The average time to AF cardioversion following the addition of the drug(s) to the perfusate was 17±15 minutes with flecainide (n=2) and 19.2±9.3 minutes with the combination of flecainide and ibutilide (n=5; p=n.s.). In one atrium in which ibutilide terminated AF, the arrhythmia terminated 7 minutes after the start of ibutilide perfusion. Following AF cardioversion with the drugs, individually or in combination, AF or atrial tachycardia could be induced in all preparations, but the arrhythmias were short-lasting (commonly terminating within 10 s after induction).

Drug-induced cardioversion of AF was always preceded by a slowing of AF CL, commonly with converting AF to atrial tachycardia (Figure 6). Following arrhythmia termination, there was a rate-dependent depression of excitability that is likely the mechanism of AF cardioversion by flecainide and flecainide plus ibutilide (Figure 6). The shortest S_1-S_1 allowing 1:1 activation was 118±21 ms following the termination of AF by the combination of flecainide and ibutilide (n=5). In the presence of acetylcholine alone, the shortest S_1-S_1 allowing 1:1 activation was ≤80 ms (this parameter could not be precisely determined due to a high incidence of AF induction at a pacing CL ≤80 ms).

Experimental Series III (LV Wedge Preparations)

Ibutilide (50 nmol/L) caused significant prolongation of APD_{90} and QT intervals in the LV wedge preparations (Figures 7 and 8). T_{peak}-T_{end} intervals, reflecting transmural dispersion of repolarization, were also dramatically prolonged by ibutilide (Figures 7 and 8). The addition of flecainide (1.5 µmol/L) caused an abbreviation of all of these parameters (Figures 7 and 8). The TdP score was 0 in the absence of the drug; the score increased to 4 in the presence of ibutilide and dropped to 1 following the addition of flecainide to the perfusate containing ibutilide.

DISCUSSION

Our experimental results demonstrate that a combination of flecainide and ibutilide possesses an additive or synergistic effect to terminate and prevent the recurrence of AF. Moreover, the drug combination has no or a low probability

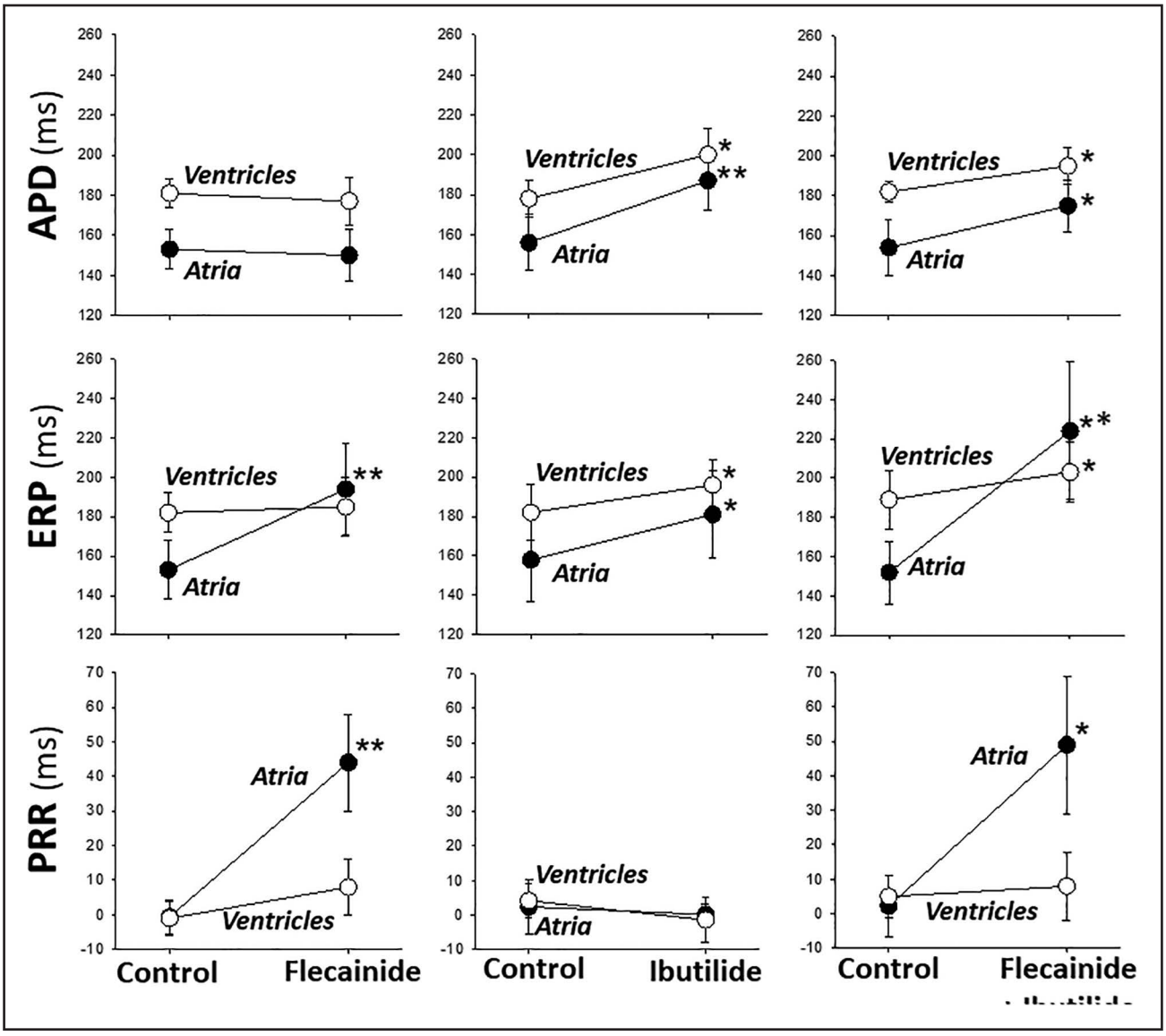

Figure 2. Effect of flecainide (1.5 µmol/L) and ibutilide (20 nmol/L) alone and in combination on atrial and ventricular action potential duration (APD_{70} in atria and APD_{90} in ventricles), effective refractory period (ERP), and postrepolarization refractoriness (PRR).

N=5 for each condition. Cycle length, 500 ms. The data were obtained from right atrial preparations with a rim of the right ventricle. *<0.05 vs control. **P<0.01 vs control.

of causing long-QT–mediated ventricular arrhythmias in our experimental setting. In the clinic, ibutilide and flecainide, when used separately, convert paroxysmal AF to sinus rhythm in 30% to 50% of patients versus placebo.[1,4] Ibutilide has been reported to induce TdP in up to 8.3% of patients.[2,11] We postulate that the combination of flecainide and ibutilide may additively or synergistically cardiovert AF and prevent its recurrence compared with monotherapy with little to no risk of TdP in patients with AF.

Efficacy and Safety

Prolongation of atrial ERP is generally a reliable surrogate for the anti-AF efficacy of antiarrhythmic drugs.[12–14] Class III agents increase atrial ERP by prolonging APD, whereas class IC agents largely prolong atrial ERP by inducing PRR.[13,14] It is expected that the flecainide and ibutilide combination would cause a greater atrial ERP prolongation than monotherapies, translating to a greater anti-AF efficacy of this combination than monotherapies in the clinical setting, as in our experimental study (Figures 2 and 4).

Although promising,[9,15,16] use of combinations of antiarrhythmic drugs for rhythm control management of AF has not been comprehensively studied.[17] Flecainide is a class IC agent that potently blocks both peak and late sodium channel currents (peak I_{Na} and late I_{Na}, respectively)[7,18] and weakly inhibits the rapidly activating

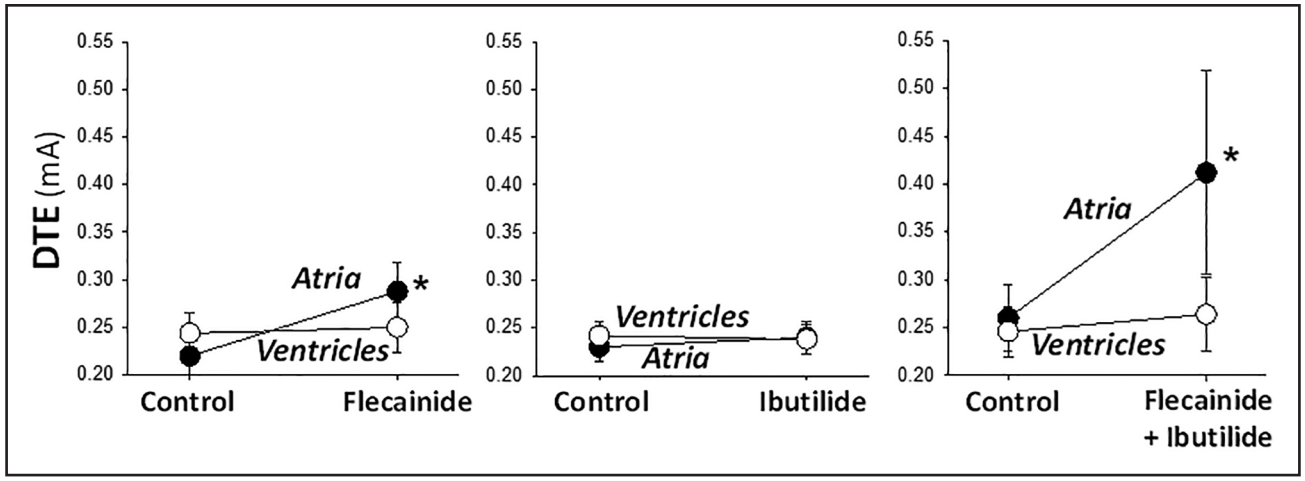

Figure 3. Effect of flecainide, ibutilide, and their combination on the atrial and ventricular diastolic threshold of excitation (DTE). N=5 per each condition. Cycle length, 500 ms. The data were obtained from right atrial preparations with a rim of the right ventricle. *<0.05 vs control.

delayed rectified potassium current (I_{Kr}).[19] Flecainide also blocks the ryanodine receptor.[20] Ibutilide, a class III agent, inhibits I_{Kr}[21] and enhances late I_{Na}.[22] The rationale for testing the combination of flecainide and ibutilide stemmed from the fact that flecainide due to its inhibition of both peak and late I_{Na} would be expected to prolong ERP, thus adding to the anti-AF effects of ibutilide while limiting excessive prolongation of ventricular APD, thus preventing the long-QT–mediated torsadogenic effect of ibutilide.[1,4] Likewise, the prolongation of atrial APD by ibutilide is expected to augment the increase in ERP by flecainide (Figure 2), thereby enhancing the anti-AF effect of flecainide. Note that I_{Kr} inhibitors increase the effect of I_{Na} blockers on the sodium channel–mediated parameters by decreasing diastolic interval (ie, reducing the recovery time), secondary to the prolongation of APD.[23] Hence, the combination of the 2 drugs would be expected to increase the anti-AF efficacy compared with monotherapies while protecting against the development of acquired long QT and TdP. The present study provides experimental evidence in support of this hypothesis.

The safety of anti-AF agents is critical in the clinical management of patients with AF. The safety and efficacy of both flecainide and ibutilide for acute cardioversion of episodes of AF have been extensively reported,[1,2] and the recommendation(s) for their use and respective contraindications have been reviewed in medical guidelines.[3] For example, there is a known risk of flecainide-inducing ventricular proarrhythmia in patients with myocardial ischemia and structural heart disease.[1] Yet, flecainide is generally safe in patients without significant structural heart

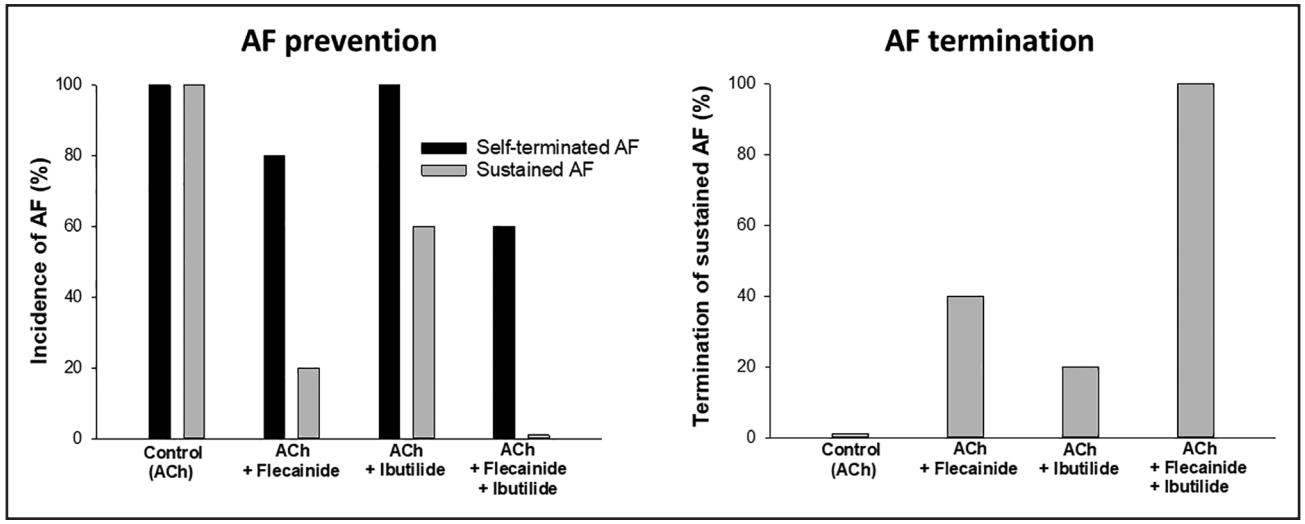

Figure 4. Prevention and termination of acetylcholine (ACh)-mediated atrial fibrillation (AF) by flecainide (1.5 μmol/L), ibutilide (20 nmol/L), and their combination.
N=10 for control and n=5 for each tested drug and the drug combination. The data were obtained from right atrial preparations with a rim of the right ventricle.

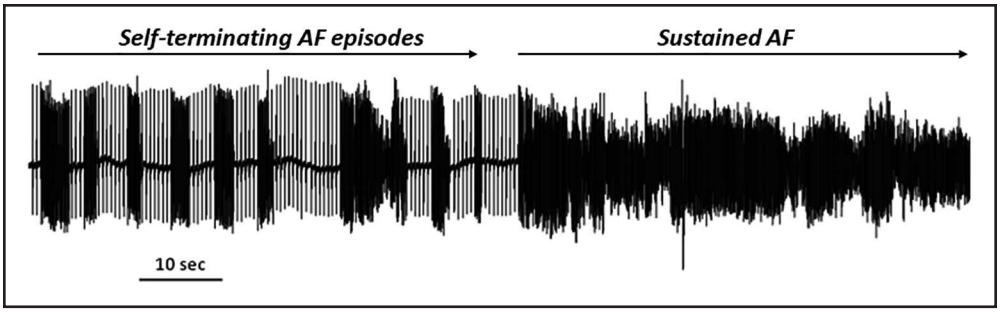

Figure 5. An example of self-terminating atrial fibrillation (AF) episodes preceding the induction of a nonself-terminated AF (lasting >1 h) in the presence of acetylcholine (0.5 µmol/L).
All AFs were induced by a single premature stimulation. Shown is a pseudo-ECG recording. The data were obtained from right atrial preparations with a rim of the right ventricle.

disease.[1] More recently, the safety of flecainide in patients with nonobstructive and stable coronary artery disease has been reported.[24–26] The use of ibutilide is associated with a substantial risk of acquired long-QT syndrome and associated life-threatening tachyarrhythmias.[2] In our experiments, the TdP score increased from 0 in control to 4 in the presence of ibutilide and dropped to 1 following the addition of flecainide, denoting no or low risk for the development of TdP with the drug combination.[10] The electrophysiological protection mechanism of the drug combination against TdP is most likely due to the action of flecainide to inhibit late I_{Na}.[7] Inhibition of late I_{Na} under conditions of reduced repolarization reserve (ie, due to reduction of I_{Kr} and augmentation of late I_{Na}) acts to protect against the risk of excessive prolongation of QT and induction of TdP.[5,6]

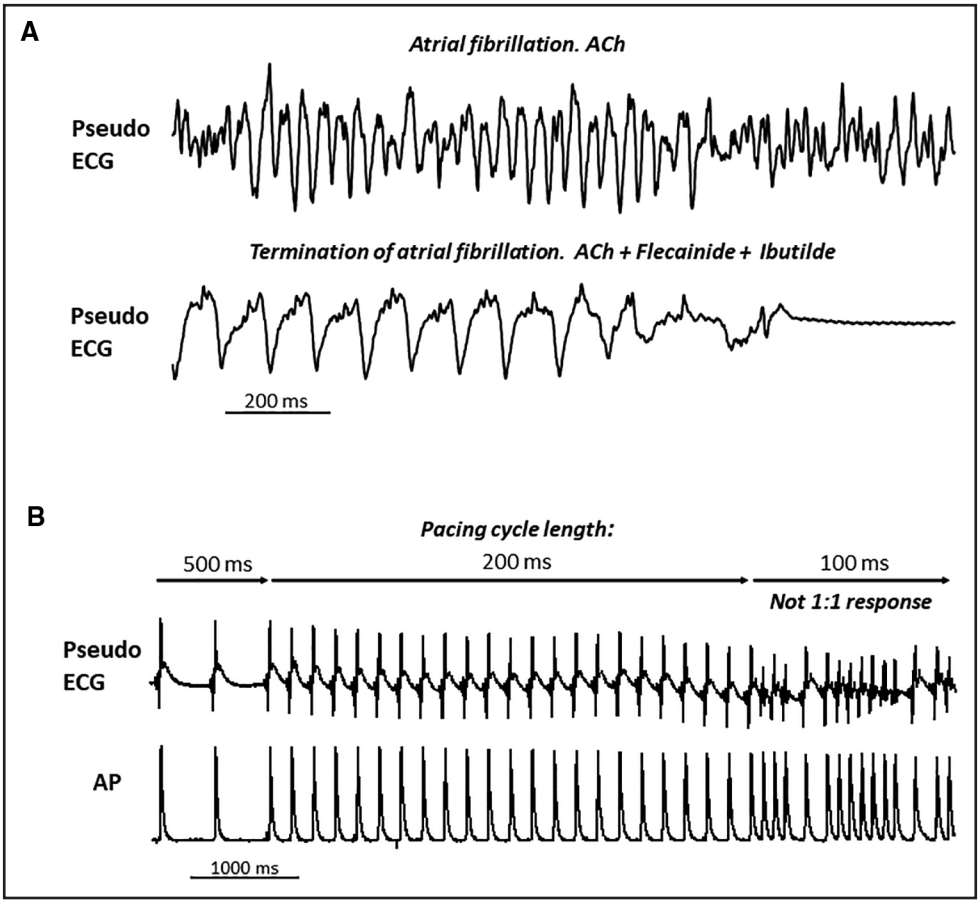

Figure 6. Drug-induced cardioversion of atrial fibrillation (AF) and its mechanism.
A, A typical example of AF cardioversion by the flecainide and ibutilide combination. AF cardioversion was preceded by the conversion of AF to atrial tachycardia. **B**, Apparent prime mechanism of AF termination with flecainide and ibutilide combination: rate-dependent depression of excitability. The recordings were simultaneously obtained following the termination of AF (in the presence of acetylcholine [ACh]+flecainide+ibutilide). The data were obtained from right atrial preparations with a rim of the right ventricle. AP indicates action potential.

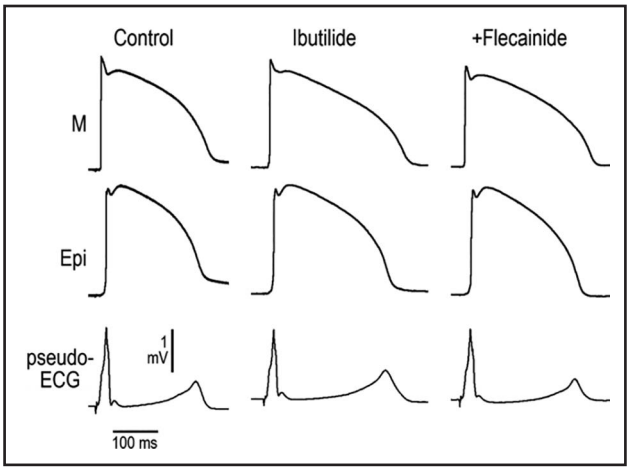

Figure 7. Representative midmyocardial (M) cell and epicardial (Epi) action potentials and pseudo-ECG recordings simultaneously obtained from a left ventricular wedge preparation under control conditions, after ibutilide (50 nmol/L), and following the addition of flecainide (1.5 µmol/L) to the perfusate containing ibutilide.
Cycle length, 2000 ms.

Clinical data on the combination of class IC and III antiarrhythmic agents for cardioversion and prevention of AF are limited. Hongo et al[27] reported the efficacy and safety of IV ibutilide to acutely cardiovert AF and atrial flutter in 71 nonresponder patients receiving class IC agents long-term (oral flecainide or propafenone; daily for >3 months). Ibutilide was shown to cardiovert AF/atrial flutter in 48% of these patients (within 1 hour). This was within the range of AF/atrial flutter cardioversion reported with ibutilide alone.[4,28] However, one patient developed sustained TdP and another nonsustained polymorphic VT following ibutilide administration and AF cardioversion.[27] In these 2 patients, ibutilide caused a significant QT prolongation (to QT values ≥500 ms versus 437±62 ms on average in all patients).[27] The incidence of adverse effects with the use of ibutilide on top of class IC agents was similar to that with ibutilide alone.[27] It is noteworthy that the administration of class I agents was chronic (daily pills) and not simultaneous with IV ibutilide. Considering these factors and a much briefer T_{Max} for IV ibutilide (minutes) versus oral flecainide/propafenone (hours), ibutilide plasma concentration is expected to be relatively high compared with that of the class I agent soon after ibutilide administration, resulting in an increased risk of ventricular proarrhythmia. It seems that for optimal efficacy and safety in the clinic, the application of ibutilide and flecainide combination should be designed to significantly overlap the concentration levels of the drugs in blood. In this study, ibutilide increased QTc by a mean of 20 ms,[27] generally less compared with that resulting from the administration of ibutilide in the absence of sodium channel blockers in other investigations (in the range of 20–90 ms).[4,11,29] This attenuation of ibutilide-induced QT_c prolongation was attributed to the inhibition of late I_{Na} by flecainide.[27] In another study, IV administration of ibutilide rapidly cardioverted AF/atrial flutter (with a mean time of 39 min) in 66% of patients (67/104) in whom oral propafenone had not cardioverted the arrhythmias (propafenone was administrated at time 0 and 6 hours and ibutilide was administrated at 8 hours).[30] Only 1 of these 104 patients developed a nonsustained episode of TdP.[30] Reiffel et al.[31] investigated the effect of IV ibutilide on QTc in patients in whom therapy with class IC agents (propafenone or flecainide; pills once a day) had been initiated (for purposes of sinus rhythm maintenance) and steady state had been achieved. In this study, pretreatment with class IC agents reduced the ibutilide-induced prolongation in QTc, and it was attributed to the inhibition of late I_{Na} by the class IC agents.[31]

Atrial Selectivity and Ventricular Proarrhythmia

In our current and previous studies,[32] flecainide caused atrial selective prolongation of ERP and depression of excitability in healthy canine cardiac preparations, comparable to those caused by ranolazine.[8] The combination of flecainide and ibutilide produced even more impressive atrial selective alteration of these sodium channel-mediated parameters (Figures 2 and 3). In our previous experience, I_{Na} blockers causing atrial-selective depression of sodium channel–mediated parameters (such as ranolazine and amiodarone)[8,33,34] have no or little risk of ventricular proarrhythmia, including in the setting of structural heart disease.[13,35] This is apparently due to the relatively mild effects of atrial-selective agents on ventricular sodium channel-mediated parameters.[8,33,34] Propafenone is less atrial-selective, causing a major depression of sodium channel–mediated parameters in the ventricles,[36] and propafenone is known to induce ventricular proarrhythmia in structurally compromised hearts.[3] Flecainide can cause ventricular proarrhythmia in patients with ischemic and structural heart disease,[1] despite causing atrial selective depression of sodium channel-mediated parameters (Figures 2 and 3). Class IC agent-induced proarrhythmia remains poorly understood. The risk of induction of ventricular proarrhythmia by class IC agents may be related to the superimposition of acute ischemia on structural heart disease.[1]

Limitations

Our experiments were conducted in isolated nonremodeled canine cardiac preparations perfused with Tyrode or Krebs-Henseleit solution. Thus, numerous factors/conditions commonly present in patients with AF (such as autonomic influences and atrial electrical and structural remodeling) cannot be assessed in our preparation, and hence, the interpretation of the data here described should take these limitations into account. Another limitation of our study is that we did not assess

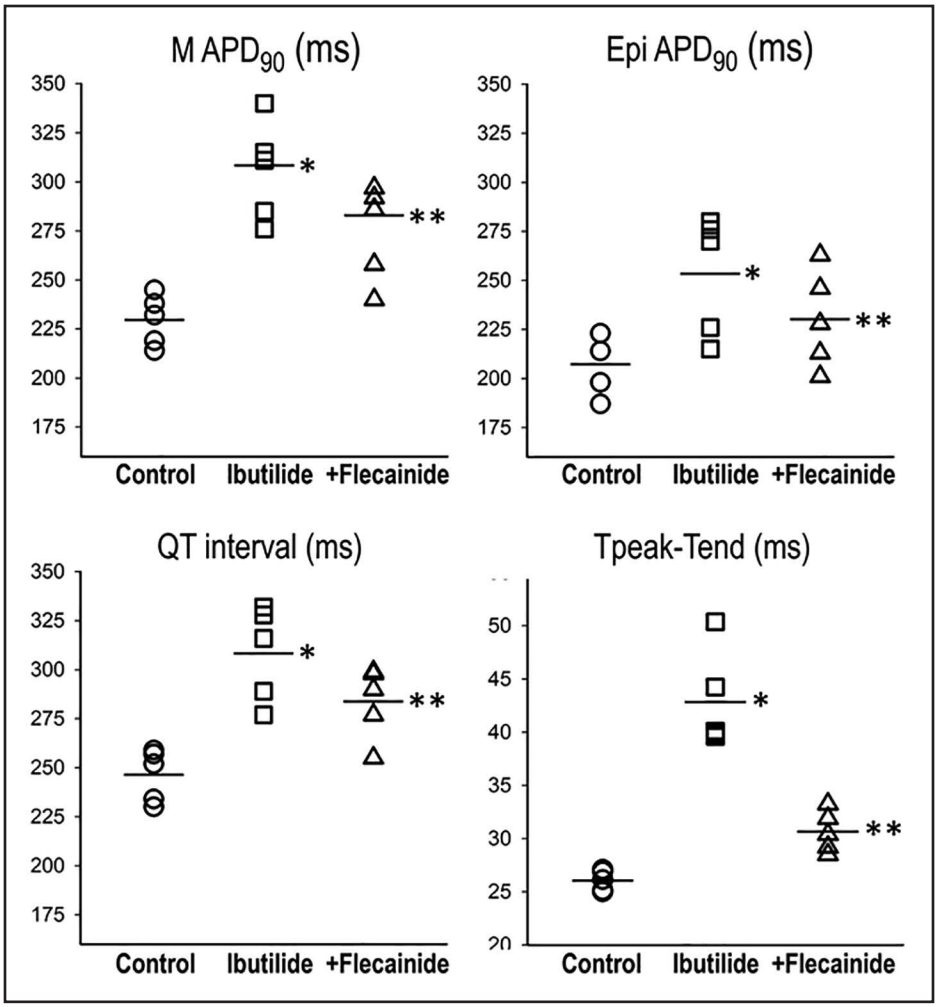

Figure 8. Effect of ibutilide (50 nmol/L) following by the combination of ibutilide (50 nmol/L) and flecainide (1.5 µmol/L) on repolarization and electrocardiographic parameters in left ventricular wedge preparations.
The symbols in each graph are individual data points, and the horizontal lines indicate the mean values. N=5 for each. Cycle length, 2000 ms. Epi indicates epicardial region APD_{90}; and midmyocardial action potential duration (M APD_{90}), M cell region APD_{90}. *P<0.05 vs control and vs ibutilide. **P<0.05 vs ibutilide.

the negative inotropic effect of flecainide, which is a safety concern in patients who undergo acute cardioversion of AF. It would have been relevant to investigate this potential adverse action of flecainide in the presence of ibutilide.

CONCLUSIONS

Our experimental data demonstrate that a combination of flecainide and ibutilide significantly improves pharmacological cardioversion of AF and prevention of AF recurrence compared with monotherapies, and this combination has little or no risk of long-QT–mediated ventricular proarrhythmia. We propose that the combination of flecainide and ibutilide could be safer and more effective than the individual drugs alone to terminate episodes of recent onset AF and prevent AF recurrences in patients without significant structural heart disease.

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Drs. Belardinelli and Echt are employees of InCarda Therapeutics, Inc. The other authors report no conflicts.

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