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Termination of a Tachyarrhythmia by Flunarizine is Not a Specific Marker for a Triggered Mechanism

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Abstract

Background—Prior studies indicated that tachyarrhythmia termination by flunarizine demonstrates a triggered mechanism. This concept was not confirmed in atrial tachyarrhythmias.

Objective—We tested the hypothesis that flunarizine will not terminate reentrant atrial flutter (AFL).

Methods—We administered flunarizine (2 mg/kg i.v. over 2 min) in 11 episodes of reproducibly inducible, sustained AFL in 8 canines with sterile pericarditis. If flunarizine terminated AFL, we studied AFL reinducibility. We also studied pacing thresholds, refractoriness, and intraatrial conduction time during closed chest studies, pacing at selected cycle lengths (CL) from selected sites before and after flunarizine. Atrial mapping (510 electrodes) assessed the epicardial activation sequence during AFL and its termination in 6 episodes. Four AFL episodes were studied in the closed chest state.

Results—Flunarizine increased AFL CL in all episodes (mean 21 ms, range 7–49), explained by slowing conduction in the AFL reentrant circuit, principally in the area of slow conduction. AFL was terminated in 10/11 episodes following drug initiation (mean 3.7 min, range 0.5–6.5) by block in the area of slow conduction. AFL was then not immediately re-inducible until >20 minutes after drug administration. Flunarizine had no meaningful effect on atrial pacing thresholds for capture or refractoriness, and only affected conduction time in the area of slow conduction in the reentrant circuit.

Conclusions—Flunarizine 1) causes progressive slowing and block in the area of slow conduction of the AFL reentrant circuit in the canine sterile pericarditis model; 2) is effective in terminating reentrant AFL, so that it is not a specific marker for a triggered mechanism.

Keywords

flunarizine; triggered rhythms; reentrant rhythms; atrial flutter

Introduction

Flunarizine, a difluorinated piperazine derivative, has been shown to block L-type and T-type calcium channels, and is thought to block accumulation of intracellular calcium selectively during calcium overload (1–3). However, the exact mechanism of its action remains unclear.

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Flunarizine is usually classified as a calcium overload blocker, but besides its activity on the calcium channels (T-, L- and N-type [4–7]), it has also been reported to affect several other ion currents, including sodium (8,9), and potassium (10).

Flunarizine has undergone clinical trials in several therapeutic areas, including migraine headache prophylaxis, peripheral vascular disease, and vertigo (1). In addition, in animal models, flunarizine has been shown to abolish ouabain- and catecholamine-induced delayed afterdepolarizations in vitro in isolated rat cardiac myocytes (11), and to terminate triggered ventricular arrhythmias in a ouabain-induced ventricular tachycardia model in the intact canine heart (12). However, flunarizine is not effective in terminating induced, reentrant ventricular tachycardia in a canine myocardial infarction model (13). Additionally, flunarizine does not affect normal or abnormal automaticity, as shown in studies of sinus rhythm and early post myocardial infarct ventricular tachycardia in canine models and barium-depolarized canine Purkinje fibers (14,15).

Based on the above observations, flunarizine has been thought to be an effective agent for discriminating tachyarrhythmias due to a triggered mechanism from those due to a reentrant or automatic mechanism (13). The specificity of flunarizine for discriminating triggered from reentrant tachyarrhythmias has not been confirmed in atrial tachyarrhythmias, although it has been used in this manner to help establish a triggered mechanism for induced atrial tachycardia in a canine heart failure model (16). Induced AFL in the sterile canine pericarditis model is a well characterized, macroreentrant tachyarrhythmia (17–21). We tested the hypothesis that flunarizine would not terminate AFL in this model.

Methods

The effects of intravenous flunarizine hydrochloride (1-[bis(4-fluorophenyl)methyl]-4-cinnamyl-piperazine, Sigma-Aldrich, St. Louis, Missouri, USA) on 11 episodes of induced, sustained (> 5 minutes) AFL in 8 adult mongrel dogs weighing 20 – 24 kg were studied 2 – 4 days after the creation of sterile pericarditis. Three dogs had an induced episode of AFL on 2 different postoperative days. In 6 dogs, atrial effective refractory periods (AERP), conduction times, and pacing thresholds were also studied from selected sites. All of the studies were performed in accordance with the guiding principles of the Declaration of Helsinki, the guidelines of the Institutional Animal Care and Use Committee, the American Association for the Advancement of Science Guidelines on the Responsible Use of Animals in Research, the American Physiological Society's Guiding Principles of the Care, and Use of Animals and the Public Health Service Policy on use of Laboratory Animals.

Creation of Sterile Pericarditis

Sterile pericarditis was created as previously described (17). Using sterile technique, the dogs underwent a right thoracotomy in the 4th intercostal space under general anesthesia (pentothal, 15 mg/kg body weight intravenously, supplemented with isoflurane). Using standard surgical techniques, the heart was exposed and cradled in the pericardium. Pairs of stainless steel wire electrodes coated with FEP polymer except for the tip were sutured to Bachmann's bundle (BB), the right atrial appendage (RAA), and the posterior-inferior left atrium (PLA). One more pair of stainless steel wire electrodes was sutured onto the right ventricular apex to be used for ventricular pacing, principally after ablating the His bundle to achieve complete AV block as part of the studies in the open chest state (22). All electrodes were brought out through the chest wall, and exteriorized posteriorly in the midline of the neck for subsequent use for pacing and recording. The atrial surfaces were then generously dusted with sterile talcum powder, a double layer of gauze was placed on the right and left atrial free walls, and the pericardiotomy was repaired. The chest was then closed in standard fashion. Antibiotics and analgesic agents were administered, and the dogs were allowed to recover.

Closed Chest Electrophysiologic Studies: Baseline (Control)

All eight dogs underwent attempts at AFL induction on postoperative days 2, 3, and/or 4. During these studies, ECG lead II and bipolar electrograms obtained from the previously placed epicardial atrial electrodes were monitored, recorded, and stored on a Cardiolab recording system (Prucka Engineering). The ECG was recorded between a bandpass of 0.1 and 500 Hz, and the bipolar electrograms were recorded between a bandpass of 30 and 500 Hz. Pacing studies were performed using a Bloom DTU stimulator. Initially, in 6 dogs, atrial pacing was performed to determine the pacing thresholds at the RAA, BB and PLA sites during pacing at cycle lengths of 400, 300, 200 and 150 ms. In addition, conduction time from each stimulus site to the other two recording sites during pacing at each of the above CLs was determined. Then, the AERP at each site was determined by introducing a premature atrial stimulus (S2) following an 8 beat atrial drive train (S1) at each of the above CLs using stimuli of twice diastolic threshold and of 2 ms duration. The initial S1-S2 interval of 80 ms was incremented by 5 ms until reliable atrial capture of the S2 was obtained. The AERP was defined as the longest S1-S2 interval that failed to capture the atria.

Closed Chest Electrophysiological Studies: Flunarizine Study Protocol

On postoperative days 2, and/or 3, and/or 4, AFL induction was attempted either using programmed electrical stimulation or burst pacing with stimuli of 2 ms duration and at least twice the diastolic threshold up to 20 mA from, in turn, each of the 3 atrial electrode sites (RAA, BB, and PLA)(17–19). Eleven episodes of sustained AFL were reproducibly (≥ 2 times) induced. Seven of these episodes were followed by open chest studies (see below). In all 11 episodes, flunarizine hydrochloride in hydroxypropyl-beta-cyclodextrin (Sigma-Aldrich, St Louis, MO, USA) was administered intravenously as a 2 mg/kg dose over 2 minutes (13,14, 16). All dogs received intravenous hydration with normal saline to prevent or minimize a potential hypotensive effect from the flunarizine administration. If AFL terminated, reinduction was attempted immediately for 2 minutes using the same pacing protocol that was used for induction. Then, the electrophysiologic studies of AERP, conduction time, and stimulus capture threshold (atrial excitability) were repeated within 10 minutes of flunarizine induced AFL termination using the protocol described above. If flunarizine failed to terminate AFL within 10 minutes, pace termination was performed, followed by a repeat of the AERP, conduction time, and pacing threshold studies. The results of these studies were compared to those prior to flunarizine administration. In 5 other episodes, sustained atrial fibrillation (> 10 minutes) was induced. When the latter occurred, flunarizine was administered using the above described protocol. Then, after termination of the atrial fibrillation, which occurred ≤ 5 minutes after the drug's administration, AERP, conduction time, and pacing threshold studies were performed as just described. The results were expressed as the mean $\pm$ standard deviation, and compared using the Student's paired t-test, with $p < 0.05$ defined as statistically significant using MS Office Excel 2003 (Microsoft Corp, Redmont, Wa, USA) and SigmaPlot 2001 (SSI, Richmond, Ca, USA).

Open Chest Studies: Simultaneous Multisite Mapping

In 7 dogs, after inducibility of sustained AFL was confirmed in the closed chest state on post operative day 2 (1 dog), day 3 (1 dog) and day 4 (5 dogs), an open chest study using simultaneous, multisite, atrial, epicardial mapping was performed prior to, during, and after flunarizine administration. Since superimposition of atrial and ventricular activation may interfere with interpretation of atrial electrograms, prior to the open chest study, His bundle ablation via a femoral approach using an EPT-1000 Cardiac Ablation System (EP Technologies, San Jose, Ca, USA) with subsequent right ventricular pacing at 100 beats per minute was performed in all experiments. The ventricular pacing rate was decreased to 60 beats per minute during mapping (22).

After the heart was exposed by a median sternotomy under general anesthesia, the electrode arrays consisting of 510 unipolar electrodes were placed on the epicardial atrial surface of both atria including Bachmann's bundle. The interelectrode distance between each bipolar electrode pair in the arrays was 0.7 mm, and the distance between the center of each bipolar electrode and its neighbor was 4.2 mm diagonally and 3.5 mm perpendicularly. The sequence of atrial activation was recorded at baseline, and both during and after flunarizine administration. Data were subsequently analyzed, and activation maps were constructed as described previously (18–20).

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

1. Effects of Flunarizine on Sustained AFL

In 11 (4 closed chest and 7 open chest) episodes of induced, sustained AFL in 8 dogs, flunarizine increased the AFL CL in all episodes (from 153 ± 18 ms to 174 ± 21 ms, $p < 0.0001$, mean increase 21 ms, range 7–49 ms) (Fig. 1), followed by AFL termination in 10 episodes after an average of 3.7 min (range 0.5–6.5 min) after the start of drug infusion. A representative example is shown in Fig. 2. In 1 episode, the AFL CL increased from 143 ms to 150 ms. This was the smallest increase in AFL CL (Fig. 1), and it was associated with failure to terminate AFL.

2. Reinitiation of AFL after Successful Termination by Flunarizine

Despite more than 10 attempts at reinduction of sustained AFL immediately following all episodes of its termination by flunarizine, AFL could not be reinduced. However, on many occasions, the pacing induction protocol did produce transient episodes (5 – 60 secs) of non-sustained AF.

Although a study of the time course of flunarizine's effect on reinducibility of AFL was not a part of the original protocol, during the course of the experiment, we did repeat attempts at AFL reinduction at a later time, i.e., not only immediately after AFL termination, but also at a time between 20 and 30 minutes after completion of flunarizine administration. At that time, we noticed that sustained AFL became inducible again, but the AFL CL was initially prolonged compared to the baseline pre-drug administration AFL CL. When this reinducible AFL was allowed to persist for another 5–10 minutes, we observed a gradual decrease of the CL, presumably as the effect of flunarizine wore off. Figure 3 shows ECG lead II and epicardial electrograms recorded from a representative example of AFL which was reinduced 20 minutes after completion of flunarizine administration, the latter having terminated the baseline AFL. Note that the AFL CL was 161 ms, longer than the baseline AFL CL (138 ms) present prior to flunarizine administration. After the reinduced AFL was allowed to persist for another 6 minutes, the AFL CL had decreased to 148 ms. We did not systematically follow any post flunarizine-reinduced AFL episodes to determine if they returned to the baseline AFL CL, although we know they approached it.

3. Open Chest Studies: Simultaneous, Multisite, Atrial Mapping

A. Termination of AFL—One episode of induced, sustained AFL was studied with simultaneous, multisite mapping in each of 7 dogs. Figures 4, 5, and 6 illustrate a representative example of the atrial activation sequence during AFL prior to and during flunarizine administration, as well as at AFL termination, respectively. In all mapped AFL episodes prior to flunarizine administration: 1) either a figure-of-eight (3 episodes) or single loop (4 episodes) (Fig. 4) right atrial reentrant circuit was demonstrated; 2) the AFL CL and atrial activation sequence were constant from beat-to-beat; and 3) an area of slow conduction was present at

an inferior pivot point in the figure-of-eight reentrant circuit or in the right atrial free wall (Fig. 4) in the single loop AFL. As illustrated in Figure 5, and in all 7 episodes, with flunarizine administration, there was progressive further conduction slowing of conduction in the area of slow conduction (demonstrated by crowding of isochrones) until termination of the AFL occurred secondary to conduction block in the area of slow conduction (Fig 6). In all episodes, the lengthening of the AFL CL was completely explained by the prolongation of conduction in AFL reentrant circuit, principally in the area of slow conduction. Atrial activation was not otherwise affected by flunarizine until AFL termination occurred.

B. Attempted Reinitiation of AFL—In all episodes following AFL termination, its reinitiation was immediately attempted, but was unsuccessful in all instances. Fig. 7 is a representative example showing the activation maps of three 100 ms windows immediately before termination of the transient AF induced by the pacing induction protocol, i.e. a failed attempt to induce AFL. The key finding was absence of development of a stable line of block between the venae cavae in the right atrial free wall, the latter being required for initiation and maintenance of the AFL reentrant circuit (19,21). A stable line of block did form after completion of the pacing induction protocol prior to flunarizine administration, resulting in sustained AFL.

4. Effects of Flunarizine on Selected Atrial Electrophysiologic Parameters

We studied the effects of flunarizine on atrial pacing threshold, AERP and conduction time (Table 1) before its administration and after its administration following 8 episodes of induced, sustained atrial tachyarrhythmias (3 episodes of AFL and 5 episodes of AF). Flunarizine did not affect AERP nor conduction time during pacing at any of the three pacing sites, nor at any pacing CL. The only change in conduction time due to flunarizine occurred during atrial flutter in the area of slow conduction in the reentrant circuit. There was a minimal increase in pacing threshold at BB when pacing at 400 ms (mean increase 0.1 mA, $p<0.001$). This change was not considered meaningful because of the small magnitude of the change, and because no other changes were observed at any other sites and pacing CLs.

Discussion

Flunarizine's effects on AFL

A principal finding of this study is that flunarizine is effective in terminating AFL due to a right atrial macroreentrant circuit. This unexpected finding contradicts the notion that termination of a tachyarrhythmia by this pharmacological agent indicates that the underlying mechanism is triggered (13). Of interest, Zhang et al. (23) suggested that the slowing of the post failed shock dominant frequency of ventricular fibrillation following flunarizine administration in their model could be explained by the presence of an intramural reentrant rhythm. If their observation and interpretation is correct, it could be consistent with our data, and could be interpreted to show that flunarizine may not be specific for triggered arrhythmias in the ventricles either.

There may be several possible explanations for the difference between the results of our study and those conducted by Vos et al. In their previously reported work, flunarizine was studied during a myocardial infarction-related reentrant ventricular tachycardia in a canine model. The antiarrhythmic effects of flunarizine in atrial tissue may differ from those in the ventricle. In addition, since blood flow in the infarcted ventricular area is impaired, suboptimal drug delivery to this area of myocardium may explain the failure of flunarizine to terminate reentrant ventricular tachycardia in this model.

Flunarizine's effects on selected electrophysiologic parameters

Flunarizine has been previously reported to exert no appreciable effect on ventricular refractoriness in canine (13) and pig (23) hearts. Our findings in the atria of our canine model are in agreement with these observations. Moreover, we did not detect any consequential change in pacing thresholds or intraatrial conduction times related to flunarizine administration, with the notable exception of conduction slowing and block in the atrial flutter reentrant circuit, principally in the area of slow conduction. In fact, the latter is another principal finding of this study.

Mechanism of flunarizine's termination of atrial flutter, and implications for the mechanism of action of flunarizine

As we have shown, flunarizine terminated atrial flutter in our model when the circulating reentrant wave front blocked in a functional area of slow conduction. Interestingly enough, the same pattern has been observed in our model when AFL terminated with administration of other pharmacologic agents (moricizine, N-acetylprocainamide, d-sotalol, flecainide), with overdrive pacing, and spontaneously (24–29).

Importantly, based on its observed effects, the efficacy of flunarizine in terminating AFL can not be explained using classic wavelength theory. Rather, our observations suggest that termination of AFL by flunarizine is most likely explained by failure of the safety factor for conduction (30), i.e., the advancing activation wavefront is not strong enough to excite the otherwise excitable tissue ahead of it in the area of slow conduction. Prior studies of propagation of activation in cardiac tissue indicate that in areas of significant conduction delay or source/sink mismatch, tissue excitability and conduction velocity depend not only on Na, but also on L-type Ca channel function (30–32) that may be affected by flunarizine. In that circumstance, it may be that flunarizine's effect on Na channels makes conduction in the area of slow conduction more dependent on L-type Ca channel function. The latter would be expected to make conduction in the area of slow conduction more vulnerable to the effects of Ca channel block. This may explain flunarizine's effect in our AFL model. But clearly, more studies are needed to fully elucidate the mechanism.

Implications of initial failure but subsequent success in reinducing AFL

As evident from the mapping studies, failure to reinduce sustained AFL after its termination by flunarizine is associated with the initial inability to form a functional line of block in the region between the venae cavae during the period of induced, but transient, atrial fibrillation. The functional line of block initially failed to develop, presumably because of the still present effect of flunarizine. This “failure” again confirms, in yet another scenario, the importance of the development of a line of functional block between the venae cavae during atrial fibrillation in order to achieve and maintain classical, right atrial, macroreentrant AFL (19,21).

Later, presumably when the effects of flunarizine diminished following completion of its bolus administration (i.e., about 20 or more minutes after completion), AFL again became inducible, but with a longer CL than at baseline. Although this reinitiation was not mapped in this study, we suggest that the reinduction of AFL with a longer CL almost surely was secondary to the fact that there was no longer enough flunarizine effect present to prevent formation of the line of block between the cavae, but enough flunarizine effect present to slow conduction in the area of slow conduction in the AFL reentrant circuit. As the drug's effects continued to diminish over time, the CL of the induced AFL continued to shorten, ultimately to that of or very close to the CL present prior to flunarizine administration.

Limitations

There are several limitations to this study:

1. We did not measure the effect of flunarizine on conduction velocity in the area of slow conduction in the AFL reentrant circuit because we could not be sure that conduction in this area was occurring in a straight line (for instance, this area was often at a pivot point), and because conduction time progressively prolonged in this area until block occurred. However, the mapping data permitted us to evaluate conduction directly, confirming that the flunarizine-induced conduction slowing was limited to the AFL reentrant circuit, principally the area of slow conduction.
2. The drug was given as a bolus over a finite time in accordance with the majority of prior studies investigating the antiarrhythmic properties of flunarizine in vivo (12-14), rather than as a continuous infusion to achieve and maintain a steady state plasma concentration of the agent. Our observation that AFL becomes reinducible about 20 or more minutes after completion of the drug's infusion suggests that the effects of flunarizine are relatively short lived. Therefore, although AERP, conduction time and pacing threshold after flunarizine administration were assessed within 10 minutes of the AFL termination, the effects of the drug may have started to diminish, thereby affecting the results of these data. Nevertheless, they are consistent with previous studies in other animal models.
3. Intravenous flunarizine has been shown to decrease systemic blood pressure (33). In this study, the animals were continuously hydrated with normal saline in order to prevent or minimize potential hypotension after the drug infusion, but no direct measurements of blood pressure were taken.
4. Although we mapped the epicardial surface of both atria, the intramural and interatrial septal activation patterns were not assessed directly. However, throughout the period of stable AFL, although its cycle length prolonged, neither the location of the reentrant circuit (mother wave) nor the atrial activation sequence by the daughter waves changed. In short, since there was 1:1 activation of all the atria from the stable AFL reentrant circuit, there is no reason to suppose that activation to any atrial area varied, including the unmapped intramural and septal areas.
5. We would like to have studied conduction more fully in the area of slow conduction before, during, and after drug administration to get more insights into the mechanism of action of flunarizine. However, using our mapping system, we could only analyze the sequence of activation data after the study. It obviously follows that we could not determine the exact location of the area of slow conduction until the study was completed (offline). Additionally, the pericarditis model does not lend itself to study using optical mapping techniques (one cannot shine a light through the inflamed tissue), nor microelectrode techniques (the glass electrodes break).

Conclusions

Flunarizine is effective in terminating reentrant AFL, and preventing its immediate reinduction. Therefore, we conclude that termination of a tachyarrhythmia by flunarizine does not necessarily indicate the presence of an underlying triggered mechanism. Also, flunarizine caused only localized electrophysiologic effects, namely progressive slowing and block of the reentrant wave front in the area of slow conduction in the AFL reentrant circuit.

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Figure 1. Effects of flunarizine on atrial flutter cycle length. Flunarizine increased the cycle length from a mean of 153 ± 18 ms to 174 ± 21 ms, $p < 0.0001$ (dashed line).

Figure 2.

ECG lead I recorded simultaneously with epicardial bipolar electrograms from the right atrial appendage (RAA), Bachmann's bundle (BB) and the posterior inferior left atrium (PLA) during atrial flutter prior to flunarizine administration, and 1 min and 4 minutes after initiating the infusion, showing gradual increase of the atrial flutter cycle length followed by its termination. AFL=atrial flutter; CL=cycle length; S=stimulus artifact; V=paced ventricular complex. See text for discussion.

Figure 3.

Delayed reinduction of atrial flutter (AFL). Panel A shows ECG Lead II recorded simultaneously with bipolar epicardial electrograms from the right atrial appendage (RAA), Bachmann's bundle (BB), and the posterior inferior left atrium (PLA) during induced AFL at a cycle length (CL) of 138 ms. After flunarizine administration (panel B), the AFL CL prolonged to 161 ms before the AFL terminated, with return of sinus rhythm after a long pause (not shown). Reinduction of AFL 20 minutes after completion of flunarizine administration (panel C) produced sustained AFL with a CL of 161 ms that shortened to 148 ms over the next 4 minutes (panel D). S=ventricular stimulus artifact; V=paced ventricular complex. See text for discussion.

Figure 4.

Left Panel: A representative epicardial activation map of the atria during induced, sustained atrial flutter (cycle length 197 ms) prior to flunarizine administration. In this and subsequent figures, the isochrones are drawn at 10 ms intervals; there is a line of functional block posteriorly on the right atrial free wall in the region of the sulcus terminalis (thin dashed gray line); the reentrant activation wave front travels down the right atrial free wall (solid, thick black arrow) and up the interatrial septum (thick dashed black arrow) to Bachmann's bundle, where it breaks through to the epicardium (asterisk) to continue again down the right atrial free wall; gray arrows represent daughter waves from the reentrant circuit (mother wave); an area of slow conduction (crowding of the isochrones) is present in the right atrial free wall; A – G are selected recording sites along the AFL reentrant circuit; RAA=right atrial appendage; LAA=left atrial appendage; SVC=superior vena cava; IVC=inferior vena cava; LSPV=left superior pulmonary vein; LIPV=left inferior pulmonary vein; RSPV=right superior pulmonary vein; RIPV=right inferior pulmonary vein, *=epicardial breakthrough. **Right Panel:** Bipolar electrograms from selected sites A–G (see left panel) in the reentrant AFL circuit. Arrows show the relative sequence of activation. See text for discussion.

Figure 5.

Left Panel: Representative epicardial activation map of the atria during atrial flutter (cycle length 229 ms) from the same episode shown in figure 4 during flunarizine administration. Note that conduction has further slowed in the right atrial free wall, as demonstrated by further crowding of isochrones. Right Panel: Bipolar electrograms from selected sites A–G (see left panel) in the reentrant AFL circuit. Arrows show the relative sequence of activation. See text for discussion.

Figure 6.

Left Panel: A representative epicardial activation map of the atria during flunarizine administration from the same episode shown in figures 4 and 5 showing termination of the atrial flutter (AFL) when the circulating reentrant wave front blocked in the area of slow conduction. Right Panel: Bipolar electrograms from selected sites A–G (see left panel) in the reentrant AFL circuit. Arrows show the relative sequence of activation. Note that AFL terminates when block (double dashed lines) occurs in the area of slow conduction between sites D and E. See text for discussion.

Figure 7.

Representative examples of transient atrial fibrillation (AF) produced by the pacing induction protocol “late” after atrial flutter (AFL) termination by flunarizine. Panel A shows a representative example in the closed chest state of a failed attempt at reinduction of AFL. ECG Lead II and epicardial bipolar electrograms recorded simultaneously from the right atrial appendage (RAA), Bachmann’s bundle (BB) and the posterior inferior left atrium (PLA) are shown during an AFL induction attempt by burst pacing from BB. This produced transient AF, which then terminated spontaneously. Panels B–D show another example of failed induction of AFL by burst pacing, but in the open chest state. Shown are the epicardial activation maps during the last 300 ms of the induced AF in 3 sequential 100 ms windows. Gray areas represent the parts of the atria not activated in a given 100 ms window. The atria are activated by multiple, unstable wave fronts with no consistent activation sequence. In the last window (panel D), all the circulating wave fronts collide and are extinguished. The key finding is the absence of the development of a stable line of block in the right atrial free wall required for AFL initiation and maintenance. See text for discussion.

Table 1

Effects of flunarizine on atrial effective refractory period (AERP), pacing thresholds, and intraatrial conduction time during pacing the right atrial appendage (RAA), Bachmann's bundle (BB), and the posterior inferior left atrium (PLA). Flunarizine did not affect atrial refractoriness at any site, nor conduction time to any site at any pacing cycle length (CL). It only minimally increased the pacing threshold at the Bachmann's bundle site (mean increase 0.1 mA) only when pacing at a cycle length of 400 ms. See text for discussion. Prior = prior to flunarizine administration; post = after flunarizine administration; * = $p < 0.001$.

AERP (ms)	RAA	BB	PLA	p	post	p	post	p	post	p	post
CL (ms)	prior	prior	prior	p	post	p	post	p	post	p	post
400	146±17	141±13	154±21	0.39	148±20	0.51	154±40	147±25	0.53		
300	145±19	144±19	148±14	0.79	149±14	0.53	139±30	138±31	0.92		
200	131±6	135±13	129±12	0.24	135±10	0.21	135±23	133±23	0.64		
150	111±11	113±12	107±10	0.76	109±7	0.72	114±16	109±13	0.26		
Pacing Threshold (mA)											
400	0.80±0.3	0.98±0.5	0.39±0.2	0.18	0.49±0.2	<0.001	1.34±0.9	1.59±1.2	0.12		
300	0.81±0.3	0.95±0.6	0.46±0.3	0.31	0.50±0.2	0.28	1.39±0.9	1.59±1.3	0.26		
200	1.00±0.6	1.06±0.7	0.50±0.3	0.24	0.59±0.4	0.13	1.55±1.1	1.78±1.4	0.15		
150	1.65±1.3	1.76±1.4	0.94±0.6	0.43	1.08±0.7	0.28	2.66±3.0	3.30±3.0	0.058		
Conduction Time (ms)											
	RAA-BB	BB-RAA	BB-BB				PLA-BB				
400	31.6±3	31.8±3	29.4±4	0.68	32.3±6	0.19	39.6±5	41.0±6	0.13		
300	31.0±4	31.8±3	29.6±5	0.42	31.0±5	0.27	40.0±5	40.5±5	0.61		
200	31.5±5	31.9±3	28.8±4	0.70	30.6±5	0.16	40.0±4	40.6±5	0.64		
150	32.8±6	33.3±3	32.9±6	0.80	31.8±4	0.41	38.3±3	41.5±8	0.13		
	BB-PLA	PLA-RAA	PLA-BB				RAA-PLA				
400	37.0±3	37.0±3	64.8±3	1	65.0±3	0.4	62.5±3	63.6±4	0.12		
300	36.5±3	36.5±3	64.6±4	1	65.3±4	0.63	62.6±4	63.6±3	0.37		
200	36.4±2	36.5±2	63.8±3	0.86	65.3±3	0.27	62.6±5	63.5±4	0.45		
150	36.5±3	37.0±4	63.8±3	0.71	66.6±4	0.16	63.6±6	63.8±4	0.94		