Flecainide-induced QRS complex widening correlates with negative inotropy

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BACKGROUND The negative inotropic effect of Class IC antiarrhythmic drugs limits their use for acute cardioversion of atrial fibrillation (AF).

OBJECTIVE The purpose of this study was to examine, in an intact porcine model, the effects of pulmonary and intravenous (IV) administration of flecainide on left ventricular (LV) contractility and QRS complex width at doses that are effective in converting new-onset AF to sinus rhythm.

METHODS Flecainide (1.5 mg/kg bolus) was delivered by intratracheal administration and compared to 2.0 mg/kg 10-minute IV administration (European Society of Cardiology guideline) and to 0.5 and 1.0 mg/kg 2-minute IV doses in 40 closed-chest, anesthetized Yorkshire pigs. Catheters were fluoroscopically positioned in the LV to monitor QRS complex width and contractility and at the bifurcation of the main bronchi to deliver intratracheal flecainide.

RESULTS Peak flecainide plasma concentrations (C_{max}) were similar, but the 30-minute area under the curve (AUC) of plasma levels was 1.4- to 2.8-fold greater for 2.0 mg/kg 10-minute IV infusion than for the lower, more rapidly delivered intratracheal and IV doses. AUC for LV contractility (ie, negative inotropic burden) was 2.2- to 3.6-fold greater for 2.0 mg/kg 10-minute IV dose than for the lower, more rapidly delivered doses. QRS complex widening by flecainide was highly correlated with the decrease in LV contractility (r^2 = 0.890, P < .0001, for all IV doses; r^2 = 0.812, P = .01, for intratracheal flecainide).

CONCLUSION QRS complex widening in response to flecainide is strongly correlated with decrease in LV contractility. Rapid pulmonary or IV flecainide delivery reduces the negative inotropic burden while quickly achieving C_{max} levels associated with conversion of AF.

KEYWORDS Atrial fibrillation; Flecainide; Left ventricular contractility; Negative inotropy; Pulmonary drug delivery; QRS complex width

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Introduction

Atrial fibrillation (AF) is a supraventricular tachycardia with a chaotic pattern of electrical activity and is associated with irregular and increased ventricular rate. This arrhythmia is the most frequently encountered rhythm disturbance in clinical practice. AF affects 5 million individuals in the United States, and its prevalence is expected to rise with aging of the population to 12 million by 2050. The mainstay therapies for acute conversion of AF include pharmacologic agents and electrical cardioversion.

Flecainide is among the most effective agents for acute termination of AF to normal sinus rhythm when delivered orally or intravenously (IV). However, these routes of administration have limitations, including necessity of high oral doses (150–300 mg) and extended (2- to 4-hour) wait times for cardioversion and the requirement of hospitalization for IV administration.

During the past decade, individuals experiencing paroxysmal AF have been increasingly managed using the “pill-in-the-pocket” method for self-administration. The experience with “pill-in-the-pocket” management has generally been favorable, with efficacy of Class IC drugs in 70% to 84% in selected patients.

Independent of the route of administration, Class I antiarrhythmic drugs share an inherent, undesirable side effect of decreasing left ventricular (LV) contractility with the potential of causing hypotension, particularly in patients with heart failure, even in those with minimum LV dysfunction. Therefore, agents such as flecainide are contraindicated in patients with heart failure.

These limitations have prompted the development of new approaches, including oral inhalation, for rapidly increasing...
antiarrhythmic drug concentration at atrial sites (INSTANT [INhalation of flecainide to convert recent onset SympTomatic Atrial fibrillation to siNus rhyThmi], ClinicalTrials.gov Identifier: NCT03539302).

Preliminary results in a phase 2 clinical study have shown promise in terms of the safety and rapidity of conversion of AF (within a few minutes) in patients with paroxysmal AF.

In a recent preclinical study, Marum et al, using an intact porcine model, examined various administration protocols to optimize flecainide plasma concentration profiles for AF conversion while minimizing adverse inotropic ventricular effects through intratracheal (IT) bolus and rapid, low-dose IV delivery. A key finding was that rapid flecainide delivery, by either IV or bolus IT injection, quickly achieved the requisite peak plasma concentration (C_{max}) for termination of the arrhythmia, with a reduced net exposure of the ventricles to flecainide. There was a corresponding reduction in the overall magnitude and duration of the flecainide-induced decrease in LV contractility following low-dose, rapid delivery via either the IV or pulmonary route.

The main goals of the current study were to extend these findings, to discuss the relationship between the pharmacokinetics of flecainide delivery and its impact on QRS complex width and LV contractility, and to present the new concept of negative inotropic burden. We defined negative inotropic burden as the product of the magnitude and duration of the flecainide-induced decrease in LV contractility (dP/dt_{max}) below predrug baseline, as measured by the area under the curve (AUC). We hypothesized that rapid delivery of flecainide would optimize achieving therapeutic C_{max} while reducing the net exposure of the ventricles to the drug. As a result, the negative inotropic burden would be reduced by minimizing the period of QRS complex widening and the attendant electrical and mechanical dyssynchrony. This hypothesis was tested using different clinically relevant doses of flecainide solutions and varied administration rates and routes.

Methods

Experimental preparation

This study conformed to the National Institutes of Health Guide for the Care and Use of Laboratory Animals as well as to the Declaration of Helsinki. The protocol was approved by the Institutional Animal Care and Use Committee of Beth Israel Deaconess Medical Center (Boston, MA). The studies were performed in 40 male Yorkshire pigs weighing 38 ± 1 kg. Details regarding the animals, anesthesia, experimental setup, and flecainide formulations tested are included in the Supplement Material.

Flecainide solutions

Various formulations of flecainide were prepared by dilution of premade solutions of 75 mg/mL concentration in sterile water and were used for both IV and IT administration.

Study protocols

Flecainide was delivered via IV infusion or IT instillation. Electrocardiographic measurements of atrial depolarization (P, dP/dt_{max}, MAP), QRS complex width, LV dP/dt, and mean arterial pressure (MAP) were obtained at 0, 2, 5, 10, 15, and 30 minutes during atrial pacing at 140 bpm.

In the IV administration experiments, flecainide (20 mL of 0.5 or 1.0 mg/kg concentration over 2 minutes or 20 mL of 2.0 mg/kg concentration over 10 minutes) was infused at a constant rate via a 7F sheath inserted into the femoral vein using a syringe pump. The 2.0 mg/kg 10-minute IV flecainide dose is the European Society of Cardiology guideline dose and rate of administration.

In the IT administration experiments, flecainide 2-mL bolus of 1.5 mg/kg formulation was followed by 3 mL of air in a 5-cm³ syringe. Additional data analyses were performed based on previous 1.0 and 2.0 mg/kg IV and 1.5 mg/kg IT experiments.

Plasma samples

Blood samples were drawn from a 7F sheath placed in the jugular vein and through the LV pigtail catheter into sodium heparin tubes at 0, 2, 5, 10, 15, and 30 minutes after the start of IV or IT flecainide administration. All samples were centrifuged and frozen at −80°C.

Chemical analysis

All plasma samples were analyzed using a high-performance liquid chromatography tandem mass spectrometric assay at Climax Laboratories, Inc. (San Jose, CA).

Statistical analysis

Statistical analyses were performed using XLSTAT (Addinsoft, Inc., New York, NY). To investigate the statistical significance of the difference between the predrug baseline values of P_{as}, QRS complex width, LV contractility (LV dP/ d_{max}), and MAP and the values after flecainide administration, repeated measures analysis of variance (ANOVA) with post hoc Dunnett test was performed. One-way ANOVA with post hoc Tamhane T2 test was performed to compare the effects of different doses. Linear regression analysis was used to compute the correlation between QRS complex widening and changes in LV contractility. Data are reported as mean ± SEM. Statistical significance was assumed at P < .05.

Results

Flecainide plasma concentration profile

C_{max} did not differ significantly among the groups. However, for the 0.5 and 1.0 mg/kg 2-minute IV injections and the 1.5 mg/kg IT bolus instillation, T_{max} occurred at 2 minutes, whereas for the 2.0 mg/kg 10-minute IV infusion, T_{max} occurred at 10 minutes, all at the sampling time points nearest to completion of drug administration.

The AUCs of the plasma concentration profiles of flecainide were 65% (P < .0001), 42% (P = .005), and 27% (P = .6) lower for the 0.5 and 1.0 mg/kg 2-minute IV doses compared to the 1.0 mg/kg 10-minute IV injection, indicating the significantly faster absorption of the bolus injections.
Absence of Effects on MAP
MAP was not significantly altered after any of the flecainide doses compared to predrug baseline. Specifically, minimum MAP after the 2.0 mg/kg 10-minute IV dose was 101 ± 7 mm Hg at 10 minutes (11 ± 3 mm Hg lower than the predrug baseline MAP; \( P = .6 \)). Minimum MAPs after the 0.5 and 1.0 mg/kg 2-minute IV doses were 96 ± 7 mm Hg at 2 minutes (0 ± 4 mm Hg lower than the predrug baseline MAP; \( P = 1 \)) and 105 ± 8 mm Hg at 2 minutes (6 ± 2 mm Hg lower than the predrug baseline MAP; \( P = 1 \)). Minimum MAP after the 1.5 mg/kg IT bolus dose was 106 ± 7 mm Hg at 2 minutes (9 ± 3 mm Hg lower than the predrug baseline MAP; \( P = .9 \)).

Atrial depolarization duration
There was a close relationship between the plasma flecainide concentration and the effects on atrial depolarization prolongation (Figure 2). Timing of the peaks in \( P_a \) duration coincided with \( T_{\text{max}} \) at 2 minutes for the 0.5 and 1.0 mg/kg IV and the 1.5 mg/kg IT bolus instillation, respectively, compared to the 2.0 mg/kg 10-minute IV infusion (Figure 1).

Effects on QRS complex width
Widening of the QRS complex after flecainide delivery also followed the time course of plasma concentrations of the drug (Figure 3). Maximum increase in QRS complex width coincided with \( T_{\text{max}} \), which occurred at 2 minutes for the 0.5 and 1.0 mg/kg 2-minute IV doses and the 1.5 mg/kg IT bolus dose and at 10 minutes for the 2.0 mg/kg 10-minute IV dose, all at
the sampling timepoints nearest to completion of drug administration. Maximum QRS complex widening over predrug baseline was 6 ± 1 ms for the 0.5 mg/kg 2-minute IV dose (P < .001), 15 ± 2 ms for the 1.0 mg/kg 2-minute IV dose (P < .0001), 19 ± 2 ms for the 2.0 mg/kg 10-minute IV dose (P < .0001), and 13 ± 3 ms for the 1.5 mg/kg IT bolus dose (P < .0001). Pairwise comparisons between the AUC of the percent change in QRS complex width identified statistically significant differences between the 2.0 mg/kg 10-minute IV infusion and the 0.5 mg/kg (P < .0001) and 1.0 mg/kg 2-minute IV infusions (P = .003) and also between the 0.5 mg/kg 2-minute IV and the 1.5 mg/kg IT doses (P = .03).

Effects on LV contractility
The flecainide-induced changes in LV contractility followed the plasma concentration profile of the drug (Figure 4). The 0.5 mg/kg 2-minute IV flecainide infusion reduced LV dP/dt\(_{\text{max}}\) by 19% ± 3% (P = .005) at the 2-minute nadir and returned to the predrug baseline value at 10 minutes. The 1.0 mg/kg 2-minute IV infusion reduced LV dP/dt\(_{\text{max}}\) by 24% ± 3% (P < .0001) at the 2-minute nadir and returned to the predrug baseline value at 15 minutes. The 2.0 mg/kg 10-minute IV infusion reduced LV dP/dt\(_{\text{max}}\) by 40% ± 2% (P < .0001) at the 10-minute nadir and remained depressed by 24% ± 3% (P < .0001) at 30 minutes. The 1.5 mg/kg IT bolus instillation reduced LV dP/dt\(_{\text{max}}\) by 25% ± 3% (P = .002) at the 2-minute nadir and returned to the predrug baseline value at 15 minutes. Pairwise comparisons of the changes in LV contractility between predrug baseline and peak effect revealed statistically significant differences from the 2.0 mg/kg 10-minute IV dose for all of the rapidly delivered, lower doses: 0.5 mg/kg 2-minute IV dose (P < .001), 1.0 mg/kg 2-minute IV dose (P = .0007), and 1.5 mg/kg IT bolus dose (P = .004).

Negative inotropic burden
The negative inotropic burden, that is, the product of the magnitude and duration of the decrease in LV contractility
below predrug baseline, measured by AUC, of the 0.5 mg/kg and 1.0 mg/kg 2-minute IV doses and the 1.5 mg/kg IT bolus was 3.6-, 2.4-, and 2.2-fold, respectively, less than that observed with the 2.0 mg/kg 10-minute IV dose (Figure 5) while achieving a comparable C<sub>max</sub> (Figure 1).

Correlation between QRS complex widening and decrease in LV contractility
The decrease in LV contractility (Δ% dP/dt<sub>max</sub>) was strongly correlated with Δ% QRS complex width for each dose (Figure 6).

Discussion
Main findings
The current study yielded 2 main findings. The first is that the flecainide-induced increase in QRS complex width is highly correlated with the depression in LV contractility. This observation raises the possibility that QRS complex widening could be a clinically useful surrogate to monitor the negative inotropic effect of flecainide. The second finding is that the negative inotropic burden can be minimized by rapid delivery of flecainide at low doses that remain effective in converting AF to sinus rhythm. Thus, rapid delivery of flecainide, independent of route of administration (ie, pulmonary or IV), provides an efficient and potentially safer approach to achieve effective antifibrillatory C<sub>max</sub> levels while reducing the net drug delivery and thereby minimizing overall exposure of the ventricles to flecainide and the negative inotropic burden. Rapid drug administration also constitutes an effective means to increase peak atrial depolarization, which has been closely linked to the probability of AF conversion.12

Prior studies of cardiodepressant effect of flecainide
Numerous clinical studies have revealed, independent of dose and rate of infusion of flecainide or characteristics and cardiovascular status of the patients studied, that flecainide exerts a transient but significant negative inotropic effect; however, this effect is greater in patients with impaired LV function.13,14 On average, flecainide-induced decreases in LV systolic pump function (ie, left ventricular ejection fraction [LVEF]) range from 9% to 18%.14 Furthermore, in patients with normal LV function, the standard dose of flecainide (2 mg/kg, 10-minute IV infusion) induces, on average, a ~12% reduction in LVEF and transient (reversible) negative inotropic effect.6 Occasionally, much greater reductions in LV systolic function can occur, even in patients without clinical or laboratory evidence of LV dysfunction (ie, no underlying heart disease). Of note, the time course of decreases in LVEF and LV contractility and their recovery toward predrug baseline are consistent with the pharmacokinetic profile of IV flecainide, as the C<sub>max</sub> is achieved at or within a few minutes after the end of infusion followed by a rapid decline, with a distribution half-life of ~4 minutes, accompanied by recovery of LV contractility.

De Antonio et al15 studied the use-dependent effects of flecainide on electrophysiologic properties using the same model as in the current study. We found that right atrial pacing even at 180 bpm resulted in ~5-ms additional increases in QRS complex width at peak flecainide plasma levels in response to IT (1.5 mg/kg) or IV (2.0 mg/kg over 2 minutes) administration relative to the increase in QRS complex width during sinus rhythm at ~100 bpm. However, whether this additional 5-ms QRS complex prolongation could have resulted in a greater decrease in LV dP/dt was not assessed.

Current study
The present study revealed that the time course of increases in QRS complex width and corresponding decreases in LV contractility in our intact porcine model correspond closely to that observed in human studies. After IV administration of flecainide, there was a rapid rise in plasma concentration, which was reflected in a corresponding increase in QRS complex width and depression of LV contractility (Figures 1, 3, and 4, top panels). This sequence also is evident during IT administration (Figures 1, 3, and 4, bottom panels). A key observation is that the negative inotropic burden of flecainide can be attenuated by rapid administration of low doses because of the smaller AUC (Figure 5), while potentially sufficient to convert AF to sinus rhythm. The benefit of rapid delivery of low flecainide doses especially the 1.0 mg/kg IV and the 1.5 mg/kg IT doses is supported by the demonstration of a comparable increase in atrial depolarization duration (Figure 2), which is mechanistically important as atrial depolarization duration is a measure of conduction velocity in atrial myocardium and is correlated (r<sup>2</sup> = 0.96, P < 0.018) with the conversion of AF to sinus rhythm.12 An important novel finding in the present investigation is the close
correlation between QRS complex widening and decrease in LV contractility independent of dose, rate, and route of infusion (Figure 6).

Mechanistic basis for linkage between QRS complex width and LV contractility in response to flecainide

The negative inotropic effect of sodium channel blockers is due, at least in part, to inhibition of $I_{Na}$, which causes a decrease in $[Na^{+}]_i$ that in turn reduces the net uptake of $Ca^{2+}$ via the $Na^{+}/Ca^{2+}$ exchanger. Flecainide also inhibits $I_{CaL}$ with a half-maximal inhibitory concentration ($IC_{50}$) of approximately 20 $\mu$M, which may contribute to its negative inotropic effect. However, this $IC_{50}$ value of 20 $\mu$M exceeds the therapeutic plasma range of ~0.5 to 2.4 $\mu$M (~200 to 1000 ng/mL). Another potential mechanism for the negative inotropic effect of flecainide is the decrease in electrical conduction velocity in LV myocardium resulting in widening of the QRS complex and thereby in electrical dyssynchrony, as shown by van Middendorp et al in a dog model of left bundle branch block. The guiding hypothesis for these findings is that electrical and mechanical dyssynchrony is closely linked through the mechanism of excitation–contraction coupling. Thus, a mechanistic basis is provided for the close correlation between flecainide-induced widening of the QRS complex and decrease in LV contractility.

In addition to reducing negative inotropic burden, rapid delivery of low doses of antiarrhythmic agents, by producing a rapid rise in $C_{max}$, increases the probability of AF conversion. Deneer et al showed in patients with AF that the likelihood of cardioversion following an oral loading dose of flecainide was strongly dependent on the absorption rate constant $K_a$. Recently, using an intact porcine AF model with both IT and IV delivery of flecainide, we demonstrated that AF conversion can be optimized by producing a rapid rise in $C_{max}$.

Study limitations

An evident limitation of the current study is the utilization of a nonhuman species; hence, the clinical relevance of the current findings must wait until human studies are conducted. Notwithstanding this limitation, it is important to recognize that the intact pig model has been extensively used in cardiac electrophysiological and hemodynamic investigations in response to diverse simulations of clinically relevant conditions, including myocardial ischemia and infarction, and has generally been found to be informative. Because the effects of flecainide to inhibit peak sodium current and widen the QRS complex are greater at faster heart rates, it is likely that its negative inotropic effect will also be greatly enhanced. Also, the experiments were performed in pigs with normal hearts, although it is well known that the negative inotropic effects of flecainide are greater in the depressed myocardium. It will be valuable to expand the current observations to large animal heart failure models. Multiple electrode catheters placed into the LV could provide further insights into changes in intra- and interventricular conduction times caused by flecainide. Nevertheless, the changes in plasma levels, QRS complex width, and LV contractility found in the current study in response to IV administration are likely to correlate with those reported in the clinical literature on flecainide.
follow the current experiments with a protocol involving oral administration.

Conclusion
Our findings confirm and extend our observation that rapid pulmonary or IV delivery of flecainide reduces the dose required to achieve C_{max} concentrations associated with conversion of AF.2,7,18 The current study reports that the attendant decrease across time in exposure of the ventricles to flecainide reduces negative inotropic burden by both the lower, rapidly delivered IV doses and the IT dose. The finding that QRS complex widening is highly correlated with decreased LV contractility suggests that this electrocardiographic marker may provide a useful surrogate to monitor the negative inotropic effect of Class IC agents and is consistent with reports that QRS complex width is associated with the concentration of flecainide in the LV myocardium.18,27 Our findings provide further support for the clinical recommendation, albeit for different reasons, that the dose of flecainide should be reduced when the QRS complex is excessively widened.28 The present pharmacokinetic and pharmacodynamic findings with delivery of flecainide via IT instillation lend support to the rationale of clinical studies using oral inhalation of flecainide, such as the Phase II INSTANT trial, which has promising results with regard to the safety and rapidity of AF conversion in patients with paroxysmal AF.8

Appendix
Supplementary data
Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2021.04.007.

References