Fast delivery of flecainide via the pulmonary (bolus) or intravenous (rapid infusion) routes reduces atrial fibrillation conversion dose and minimizes negative inotropic burden

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Background/Introduction: The negative inotropic effect of certain antiarrhythmic drugs limits their use for acute cardioversion of new-onset paroxysmal atrial fibrillation (AF).

Purpose: In an intact porcine model of AF, we examined the effects of pulmonary and intravenous (IV) administration of flecainide on left ventricular (LV) contractility, i.e., LV dP/dt max, at doses that are effective in converting AF to sinus rhythm. The magnitude of the decrease in LV dP/dt max and time that it remained below baseline, measured by the area under the curve (AUC), is referred to as negative inotropic burden.

Methods: Flecainide was delivered via intratracheal administration at 1.5 mg/kg bolus and compared to IV infusion at 1.0 mg/kg over 2 min (lower-dose, rapid) and 2.0 mg/kg over 10 min (ESC guideline) in 11 closed-chest, anesthetized Yorkshire pigs. These doses of flecainide have been shown effective in converting AF to sinus rhythm. Catheters were fluoroscopically positioned in the right atrium for pacing at 140 beats/min and in the LV to measure QRS complex duration and contractility (LV dP/dt). Intratracheal flecainide was delivered via a catheter positioned at the bifurcation of the main bronchi.

Results: The peak plasma levels (Cmax values) were similar but the AUC of plasma concentrations over time was greater for the higher-dose, slow IV infusion of flecainide than for either intratracheal instillation (by 32%) or lower-dose, rapid IV infusion (by 88%). Based on AUCs of LV dP/dt max (figure, left panel), the negative inotropic burden is 3.1- to 3.8-fold greater for the higher IV (1006% • min) than for the lower IV (323%·min) or the intratracheal doses (263% • min). There was a corresponding inverse increase in the AUC of QRS complex prolongation. The decrease in LV dP/dt max (∆%) was correlated with the prolongation of the QRS complex (∆ms) ($y = -1.4337x + 3.6613$, $r2=0.69$, $p<0.0001$) (figure, right panel).

Conclusion: Rapid delivery of pulmonary or IV flecainide reduces the dose of drug required to achieve Cmax levels associated with conversion of AF. The attendant decrease across time in exposure of the ventricles to flecainide reduces QRS complex prolongation and the accompanying negative inotropic burden.