

# Concentration-Dependent Changes in ECG-Derived Indices of Repolarization Induced by Isoflurane: A Study in Telemetered Beagle Dogs

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## Introduction

Anesthetized animal models are used to evaluate *in vivo* electrocardiographic liability of pharmacologic compounds; however, recent evidence suggest that the choice of anesthetic may influence torsadogenic responses (1). many commonly used volatile anesthetic agents, (e.g., isoflurane) can prolong the QT-interval *in vivo* (2,3) and can alter electrophysiology *in vitro*, depressing, for example, late repolarization currents (4); these may facilitate torsadogenicity and/or induced malignant arrhythmias *in vivo*.

This study evaluated the independent electrocardiographic effects/liability of isoflurane anesthesia (ISO) *in vivo*.

*Isoflurane will prolong ECG-derived indices of ventricular repolarization, negatively affecting torsadogenic markers*

## Materials & Methods

Healthy Beagle dogs (n = 13) were instrumented with a radio transmitter that provided telemetry signals for arterial blood pressure, temperature, and ECG (D70-PCT; DSI).

Two weeks later,, anesthesia was induced with propofol, an endotracheal tube was placed and the lungs were mechanically ventilated to a PaCO<sub>2</sub> of 40 mmHg (12 breaths/min, 100-250mL). Telemetric signals were recorded before induction and after stabilization at three decreasing end-tidal isoflurane concentrations: 1.5, 1.2 and 1.0% (n = 7). In an additional group of animals (n = 6), anesthesia was induced/maintained only with isoflurane (5%, via mask), in order to evaluate any confounding/concomitant changes due to propofol administration (5,6). Subsequently, the minimum alveolar concentration (MAC) was determined for each animal (1.14 ± 0.04%).

ECG signals were analyzed offline (ECG Auto; EMKA Technologies) and differences in repolarization indices were evaluated by a RM one-way ANOVA; concentration dependence was studied by linear regression. P<0.05 was significant. Data is presented as mean ± SEM.

## Results

Isoflurane prolonged indices of repolarization-duration, such as the QTc (228 ± 4 vs. 265 ± 7 msc @1.5%) and the Tpeak-Tend (228±3 vs. 47±7 ms @1.5%) intervals, decreasing the TQ/QT ratio (2.65 ± 0.15 vs. 2.00 ± 0.14 @1.5%) (see Table 1). Moreover, isoflurane shifted the QT/RR-relationship upwards (see Figure 1); these changes were linearly predicted by the concentration of isoflurane (e.g., QTc: R=0.70 vs. ISO%, P<0.001).

It is important to note that slowed repolarization was observed even at isoflurane concentrations below-MAC (@1.0% QTc: 258 ± 7 msc and TPE: 38 ± 5 msc).

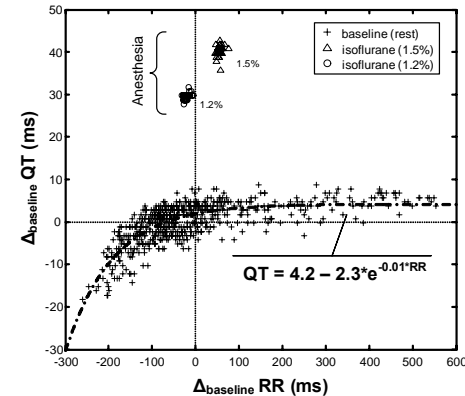
Table 1. Isoflurane-induced changes in hemodynamic and electrocardiographic parameters (n = 7)

Time	HR (bpm)	MAP (mmHg)	RR (ms)	TPE (ms)	QT (ms)	QTc (msc)
Baseline	81 ± 5	131 ± 11	764 ± 44	28 ± 3	207 ± 4	228 ± 4
ISO 1.5%	85 ± 7	66 ± 10	727 ± 50	48 ± 7	241 ± 10	265 ± 7
ISO 1.2%	85 ± 7	78 ± 10	660 ± 62	44 ± 6	231 ± 11	261 ± 7
ISO 1.0%	85 ± 7	81 ± 7	680 ± 57	38 ± 5	230 ± 10	258 ± 7

P < 0.05† ↓ ↑

†, Arrows (↓, ↑): P<0.05 isoflurane (ISO) vs. baseline (rest/awake). TPE = Tpeak-Tend; QTc = QT interval corrected for heart rate (van der Water's).

Figure 1. Representative beat-to-beat QT-RR relationships before (baseline, awake at rest) and after isoflurane anesthesia



## Results (cont.)

The electrocardiographic effects of isoflurane were observed even when no pre-anesthetic/induction agents (e.g., propofol) were used (e.g., QTc: 227 ± 6 vs. 270 ± 8 msc @1.5%, see Table 2).

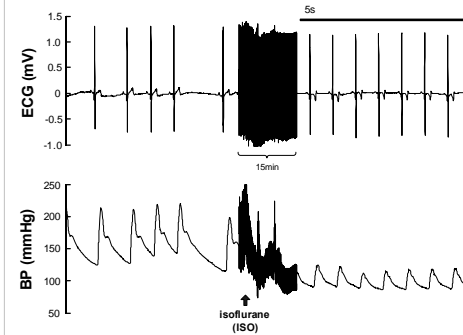
In addition, isoflurane altered T-wave morphology (e.g., amplitude: -0.43 ± 0.06 vs. -0.96 ± 0.12 mV; area: -7.2 ± 1.0 vs. -17.4 ± 2.3 mV\*s, P<0.05), suggesting increased repolarization heterogeneity.

Table 2. Isoflurane-induced changes in hemodynamic and electrocardiographic parameters (no induction agent, n = 6)

Time	HR (bpm)	MAP (mmHg)	RR (ms)	TPE (ms)	QT (ms)	QTc (msc)
Baseline	72 ± 9	127 ± 12	904 ± 87	30 ± 4	219 ± 10	227 ± 6
ISO 1.5%	84 ± 4	67 ± 10	718 ± 32	48 ± 5	246 ± 10	270 ± 8

†, Arrows (↓, ↑): P<0.05 isoflurane (ISO) vs. baseline (rest/awake). TPE = Tpeak-Tend; QTc = QT interval corrected for heart rate (van der Water's).

Figure 2. Representative ECG and arterial blood pressure tracings before (baseline, awake at rest) and after isoflurane anesthesia



## Conclusion

These results suggest that clinically relevant concentrations of isoflurane exert potent, concentration-dependent effects on electrocardiographic parameters generally used to indicate pro-arrhythmic liability.

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