Langendorff isolated heart from guinea pig or rabbit

➢ Background

Isolated rabbit heart preparation as a model for detecting changes in the QT interval has been confirmed by studies demonstrating sensitivity to drugs that prolong the rate-corrected QT -interval (QTc) in humans. The objective of this study is to evaluate the in vitro effects of [test article] on isolated rabbit hearts. The heart rate, PR-interval, QT-interval, and QRS duration of the ECG together with Left ventricular contractility will be measured.

➢ Assay specifics

- Compound profiling against the ECG from isolated heart to evaluate potential cardiac liability
- Langendorff isolated heart with the experiment temperature of 36.5°C
- Positive control and vehicle control in every assay
- Three concentration profiling with 12 pt.; n=4
- This assay is performed by PharmaCore Labs who specialize in cardiac safety assessment of preclinical drug candidates

➢ Cardiac phenotyping with the Langendorff isolated heart technique

The validity of the isolated guinea pig or rabbit heart preparation as a model for detecting changes in the QT interval has been confirmed by studies demonstrating sensitivity to drugs that prolong the rate-corrected QT -interval (QTc) in humans.

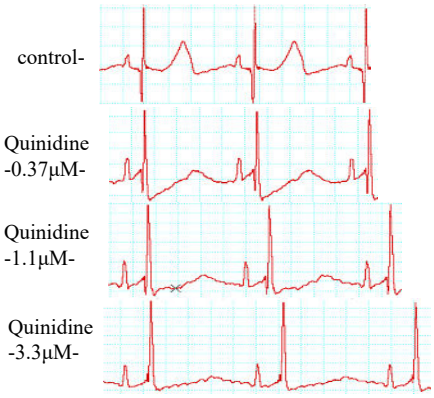
Drugs that have multi-ion channel effects are important to evaluate in isolated hearts to determine the ion channel's overlap effects on the whole heart. For example, quinidine and verapamil are both strong hERG blockers but only quinidine prolongs QTc significantly in humans. The intact isolated heart contains the tissues, receptors, and channels that may be potential targets for drugs that affect ventricular repolarization and is also a useful model for detecting the inotropic effects of drugs.

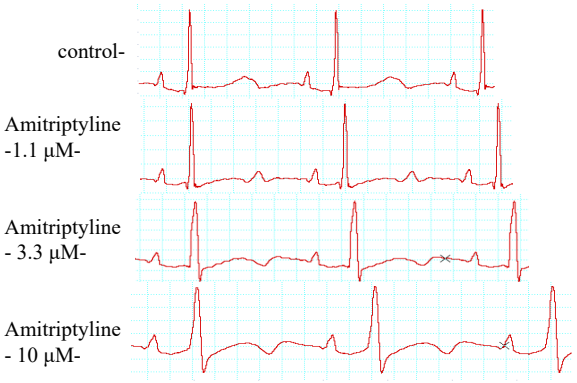
- a study example is presented on the next page -

ADME & SAFETY SERVICES

➢ The effects of multi-channel blockers on Langendorff isolated hearts

Compound	Concentration	RR (%)	HR (%)	PR (%)	QRS (%)	QT (%)	QTc (%)
Quinidine (n=4) hERG↓↓ Cav1.2↓ Nav1.5↓	0.37 μM	3.0±2.6	-2.7±2.5	2.4±2.8	10.6±3.7	20.3±10.0	18.3±9.5
	1.1 μM	14.6±3.1	-12.6±2.4	30.9±12.6	12.6±8.2	38.2±9.7**	29.2±9.3*
	3.3 μM	23.6±3.9	-18.9±2.5	32.8±17.6	13.6±6.0	44.5±11.9***	30.0±10.4*
Verapamil (n=3) hERG↓↓ Cav1.2↓↓ Nav1.5↓	0.04 μM	14.9±4.9	-10.4±8.2	-0.7±5.0	-4.3±2.6	3.7±4.6	-2.7±0.7
	0.12 μM	19.4±3.3	-15.2±9.4	5.8±13.5	-11.2±2.8	11.7±1.9	2.8±7.5
	0.37 μM	36.0±12.8**	-25.8±7.0**	5.4±9.4	-11.3±3.5	15.4±0.7	-0.6±4.0
Amitriptyline (n=3) hERG↓ Cav1.2↓ Nav1.5↓↓	1.1 μM	4.42±1.2	-4.2±0.69	3.9±0.98	12.2 ±3.6	5.4 ±3.6	3.2±2.5
	3.3 μM	8.3±1.02	-7.7±1.23	40.4±4.7	17.8±1.4	12.8±4.2	8.4 ±3.8
	10 μM	20.4±0.25	-16.9±0.25	49.91±5.3	70.0±8.24	20.1±3.8	9.4±4.7





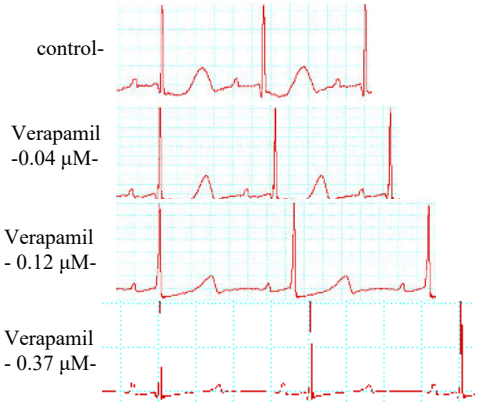


Figure 1. *Three multi-channel blockers, quinidine, verapamil, and amitriptylineas, were studied in Langendorff isolated heart assay. The table below summarized that both quinidine and verapamil significantly block hERG with IC50 less than 1 μM, however ECG results from isolated heart show verapamil's QTc prolongation is minor with less cardiac safety concern, while quinidine prolongs QTc significantly with high risk. This suggests that hERG blockers with multi-channel effects may have less cardiac risk.*

Compound	hERG	Cav1.2	Nav1.5
Quinidine	0.82 μM	5.22 μM	110 μM
Varapamil	0.49 μM	0.26 μM	41.9 μM
Amitriptyline	7.61 μM	10.4 μM	0.63 μM