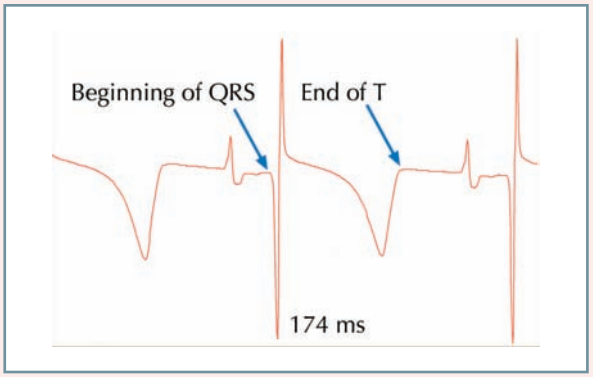
Langendorff

Rabbit or Guinea Pig Heart

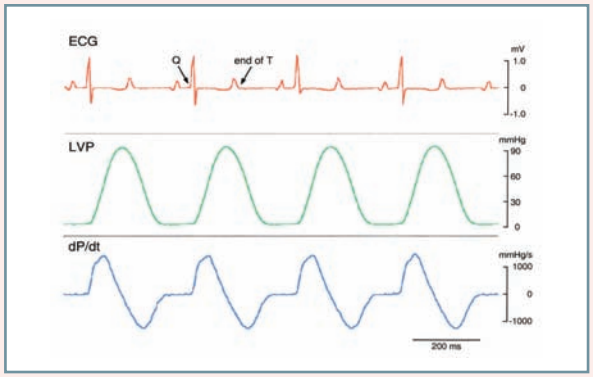
Langendorff - Informative and Economical

- Measures all important cardiac parameters with great repeatability and accuracy
- High sensitivity and specificity
- Rapid turn-around time
- Economical
- Validated acquisition and analysis systems
- GLP compliant

Isolated hearts perfused with modified Krebs and instrumented to measure bipolar, transventricular electrograms, isovolumetric left ventricular pressures and coronary flow.



Transventricular electrogram showing how precisely beginning and end of QT can be identified. A small HIS bundle electrogram can be observed in the PQ segment just before the QRS complex begins.



Recordings (from top to bottom) of transventricular electrogram, isovolumetric left ventricular pressure (LVP), and dP/dt of LVP. Because the pressure is isovolumetric with constant loading conditions, dP/dt_{max} indicates inotropy and dP/dt_{min} indicates lusitropy.

Lead optimization: Studies conducted at QTest Labs identify "lead" compounds that possess the lowest potential for developing cardiovascular toxicity.

Comprehensive assessment of all cardiovascular parameters: Test articles may produce toxicity on any or all properties of cardiovascular function (e.g., chronotropy, dromotropy, irritability, inotropy, lusitropy, vascular resistance, baroreceptor sensitivity). QTest Labs interrogates the effects of test articles on all of these properties.

Studies are performed in compliance with GLP regulations, and are compatible with ICH guidelines for safety pharmacology.

Positives

Known to lengthen QTc

test articles	molar concentrations 10^{-9}	10^{-8}	10^{-7}	10^{-6}	10^{-5}	10^{-4}	10^{-3}	N
ambasalide				0.053	** 1E-04	** 1E-04		4
desipramine				* 0.024				4
morphine					0.088	** 0.002		4
oxycodone								2
tefenadine				* 0.027	* 0.011			8
buprenorphine			* 0.023	** 0.001	** 1E-04			4
methadone								2
clozapine			* 0.031	** 3E-04	** 0.002			4
diphenhydramine			* 0.017	** 0.001	** 1E-04			4
bepridil			0.0751[a]					4
indapamide					* 0.043			4
thioridazine					* 0.038			4

test articles	molar concentrations 10^{-9}	10^{-8}	10^{-7}	10^{-6}	10^{-5}	10^{-4}	10^{-3}	N
haloperidol			0.0848[a]					4
sparfloxacin				** 0.004				4
dl sotalol					** 9E-04	** 1E-04		8
chloroquine					** 1E-04			4
bretylium		** 0.002	** 0.003	** 1E-04	** 1E-04	** 1E-04		4
erythromycin							* 0.018	4
cisapride		** 0.009	** 1E-04	** 1E-04	** 1E-04	** 1E-04		5
pimozide				* 0.018	** 0.002			6
astemizole					* 0.018	** 0.004		6
chlorpheniramine		* 0.0419[b]			** 0.008			6
disopyramide					** 1E-04	** 1E-04		6
tetracycline						** 0.009	** 7E-04	4

a: p value as a curve, b: QTc was shortened

Drugs known to lengthen QTc in man that also lengthened QTc in the guinea pig Langendorff preparation. The molar concentrations at which lengthening was observed are labeled with an asterisk. Based on this data, the sensitivity of the preparation is 1.0.

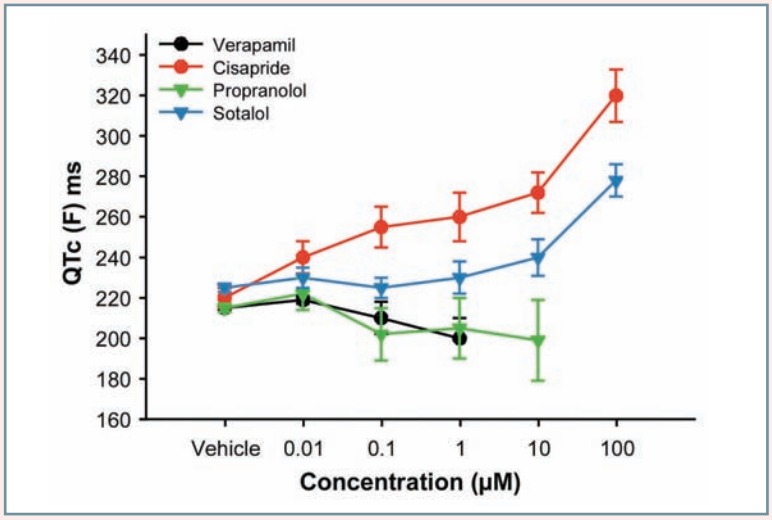
Negatives

No lengthening of QTc

test articles	molar concentrations 10^{-9}	10^{-8}	10^{-7}	10^{-6}	10^{-5}	10^{-4}	10^{-3}	N
penicillin								6
aspirin								4
captopril								4
dl propranolol								4
iohexol								2
milrinone								2
mexiletine								4
ouabain								2
zatebradine								2
cilobradine				0.0537[a]				6
enalaprilat								2
verapamil				** 0.0011[b]				4
thalidomide								4
carvedilol								2

a: p value as a curve, b: QTc was shortened

Drugs thought not to lengthen QTc in man that also failed to lengthen QTc in the guinea pig Langendorff preparation. The molar concentrations tested are shown by empty boxes. Verapamil and cilobradine shortened QTc.



Plots of QTc versus dose of 2 compounds (cisapride and sotalol) known to lengthen QTc and 2 compounds (propanolol and verapamil) known not to lengthen QTc. Sensitivity and specificity for predicting QTc are 1.0, based upon studies on over 60 compounds.

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