

The E-C coupling assay

Assay

Simultaneous action potential and mechanical tension measurements

Tissue or cell line

Guinea-pig, rabbit, dog, human ventricular trabeculae or papillary muscle

Technique

High-impedance micro-electrode and isometric tension transducer

GLP Compliance

Pre-IND (GLP-compliant) or exploratory designs (non-GLP compliant)

Rationale

The proper function of the heart depends on the integrity of its excitation-contraction (E-C) coupling - the efficiency with which the excitatory electrical impulse (the action potential) induces the proper mechanical response, the contraction of the cardiac myocytes.

Being able to simultaneously measure the action potential with the isometric tension of contractile cardiac tissues such as papillary or ventricular tissue, allows one to establish whether the delicate coupling between the excitatory stimulus and the resulting contraction.

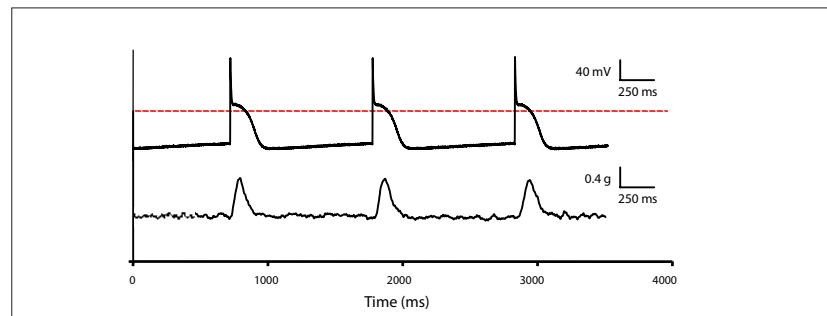


Figure 1. Simultaneous APD and contraction-relaxation measurements in dog ventricular strips

Protocol outline

Number of tissues analyzed : 5

Number of concentration of the test article per tissue : 4

Method of test article exposure : Continuous perfusion

Stimulation pattern : Electric field stimulation, 0.7 Hz

Positive controls commonly used : nifedipine, d,l-sotalol, or terfenadine

Study outcome

- A quantitative assessment of drug-induced EC-decoupling, including action potential duration and amplitude, in parallel with contraction-relaxation amplitude and kinetics
- Determination of the concentration at which de-coupling occurs (if applicable)
- FDA-ready hard-copy and e-report for electronic IND submission
- Holistic interpretation of a positive signal, considering all other existing data

Recommended readings

1. Sah R. Ramirez RJ. Oudit Gy. Gidrewicz D. Trivieri MG. Zobel C. Backx P., Regulation of cardiac excitation-contraction coupling by action potential repolarization: role of the transient outward potassium current (I_{to})., *Journal of Physiology*. 546(1):5-18, 2003.

2. Cahill SA. Kirshenbaum LA. Gross GJ., Transient outward current inhibition by propafenone and 5-hydroxypropafenone in cultured neonatal rat ventricular myocytes, *Journal of Cardiovascular Pharmacology*, 38:460-7, 2001.