

Simultaneous Assessment of CiPA Stipulated Ion Channels on the SyncroPatch 384PE

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Summary

The cardiac action potential is defined by multiple voltage-dependent ion channels (see Fig. 1). A drug candidate's capacity to interact with the ion channels involved in the depolarization or repolarization phases of the cardiac action potential is important for drug safety assessment. Until now, safety testing has focussed on interaction with the hERG channel and QT prolongation which can lead to potentially fatal torsades de pointes (TdP).

Although this approach has been largely successful in preventing new drugs reaching the market with unexpected potential to cause TdP, it is also possible that potentially valuable therapeutics have failed due to this early screening. A new paradigm, the Comprehensive In-vitro Proarrhythmia Assay (CiPA), was introduced in 2013 to provide a more complete assessment of proarrhythmic risk^{1,2}. An assessment of a multitude of cardiac ion channels, in addition to hERG, should provide a more accurate prediction of the proarrhythmic risk of a compound compared with testing on hERG alone.

Here we show recordings from HEK or CHO cells expressing the CiPA stipulated ion channels; Na_v1.5, Ca_v1.2, hERG, K_v7.1, K_{ir}2.1 or K_v4.3, activated within one single experiment on the SyncroPatch 384PE.

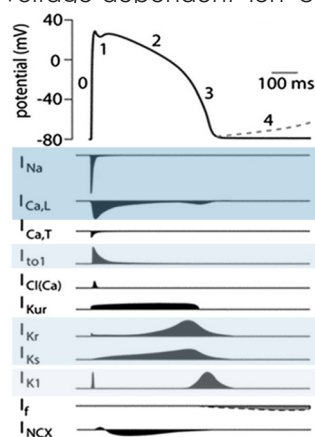


Figure 1: Cardiac action potential and underlying currents (reproduced from Ref. 2).

Results

A combined voltage step-ramp protocol (Fig. 2) was applied simultaneously to HEK or CHO cells expressing different cardiac ion channels. The first segment was used to elicit Na_v1.5 or Ca_v1.2 (1) followed by a classical hERG-like segment to activate K_v4.3, K_v11.1 and K_v7.1 (2) and finally a ramp protocol to elicit inwardly rectifying K_{ir}2.1 (3).

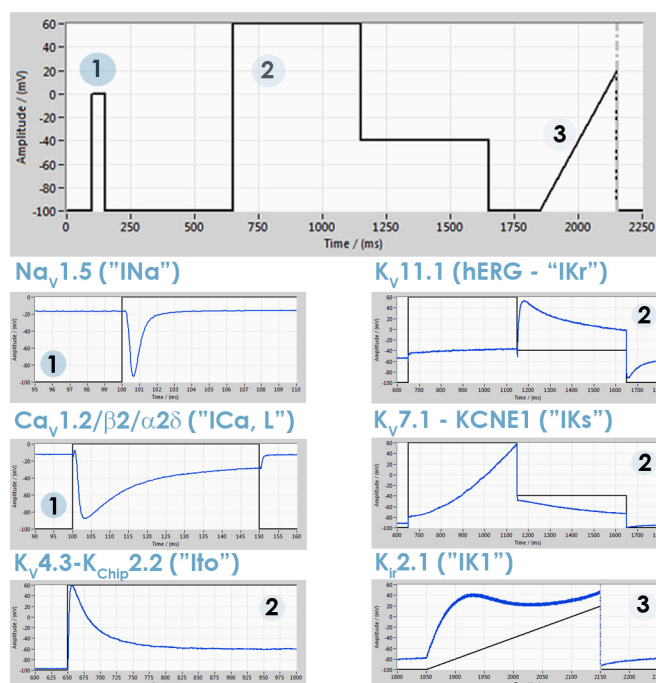


Figure 2: A voltage protocol was used to activate 6 distinct cardiac ion channels. The top panel shows the voltage protocol used on all wells to simultaneously activate the 6 distinct cardiac ion channel currents shown in the bottom panels.

Application Note

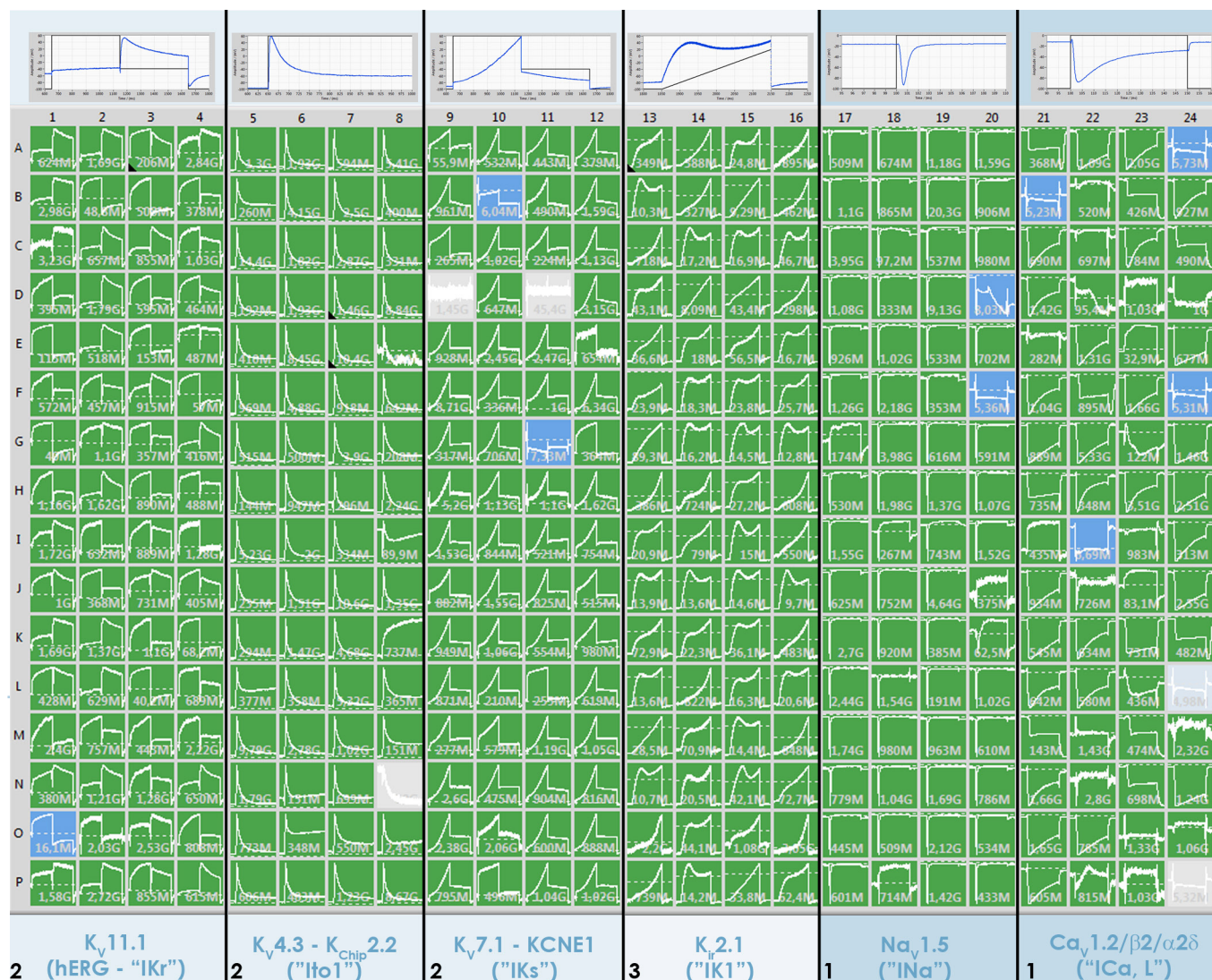


Figure 3: Six different cardiac channels recorded simultaneously on the SyncroPatch® 384PE. Shown is a screenshot of the data acquisition and analysis software used on the SyncroPatch® 384PE showing an experiment recording six different cardiac channels at once. A representative image of the current recording for each ion channel is shown at the top.

In conclusion, the SyncroPatch 384PE can be used to assess the effects of compounds simultaneously on multiple cardiac ion channels at a high throughput. These ion channels have been indicated by the CiPA initiative

to be key targets for safety testing. In this way, a more accurate risk assessment of compounds can be made taking into account a multitude of ion channels.

References

1. <https://www.ilsixtra.org/hesi/science/cardiac/cipa/SitePages/Home.aspx>
2. Sager, P.T., et al., 2014. Am. Heart J. 167(3): 292-300

Methods

Cells

CHO cells expressing Na_v1.5, Ca_v1.2, K_v4.3 or K_v7.1; HEK293 cells expressing hERG or K_v2.1 from Charles River.

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Cell culture & electrophysiology

Cells were cultured and harvested according to Nanion's standard cell culture protocols and perforated patch clamp recordings were conducted according to Nanion's standard procedures for the SyncroPatch 384PE using 20 µM Escin .