Application Note

Cells: hiPSC-CM
Tools: CardioExcyte 96

Conduction velocity with the 2-electrode layout of the CardioExcyte 96

Nanion Technologies GmbH
Cardiosight®-S hiPSC-CMs kindly provided by Nexel

NEXEL

Summary

Cardiac conduction is the process by which electrical excitation spreads through the heart, triggering individual myocytes to contract synchronously. Slowed cardiac conduction velocity (CV) is associated with an increased risk of re-entrant excitation, leading to a pre-disposition to life-threatening arrhythmias[1].

CV is determined by the ion channel properties of cardiac myocytes and by their interconnections. It is strictly dependent on the maximum upstroke velocity of an action potential, which is determined by the sodium current[2]. In addition, gap junctions play a key role because they ultimately determine how much depolarizing sodium current passes from excited to non-excited regions of the network. Uncoupling of gap junctions causes discontinuities leading to slower CV. Defective intercellular coupling between the cardiomyocytes results in increased subthreshold depolarization, which slowly inactivates the voltage-gated sodium channels, further reducing the sodium current and excitability[3].

In the case of collagenous scar tissue the uncoupling of myocyte–myocyte connections and subsequent coupling of myocytes with fibroblasts impairs the electrical conduction. In fact, collagen deposition results in electrically isolated fibers of viable myocardium, discontinuing the conduction path and globally reducing the action potential propagation velocity and consequently promoting the onset of re-entrant arrhythmias[4].

Since CV plays a pivotal role in cardiovascular diseases, it is essential to investigate the effect of a new compound on the cardiac CV.

In this study, we have investigated the effect of the sodium channel blocker lidocaine (30 and 100 µM) on CV in hiPSC-CMs (NEXEL Cardiosight®-S) using the CardioExcyte 96.

Results

To estimate the CV the time delay between the electrical pacing artifact and the maximum peak of the EFP sodium spike was calculated before and after compound addition (Figure 1A). Since the distance between the stimulation electrode and the recording electrode in the NSP-96 Stim plate is known (Figure 1B), it is possible to estimate the CV as the ratio of the distance between the two electrodes and the time delay between the pacing artifact and the peak of the sodium spike. The CV calculated with the CardioExcyte 96 is an approximation due to the presence of only two electrodes, which are simplified as two points. Therefore, the percentage change before and after compound addition is calculated, instead of an absolute CV value.

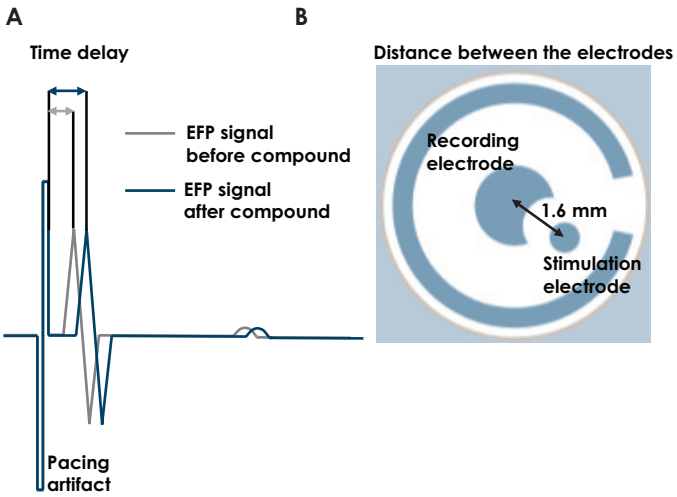

Figure 1: A) Simplified EFP signals under electrical pacing before (grey) and after (blue) compound addition. The time delay between the pacing artifact and the sodium spike peak used to calculate the conduction velocity is depicted. **B)** Distance between the recording and stimulation electrodes in the NSP-96 Stim plate.

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In control conditions, EFP signals are stable and can be overlaid when treated with vehicle (Figure 2). There is no difference between field potential duration (FPD) recorded during baseline vs. vehicle measurements (Figure 2B).

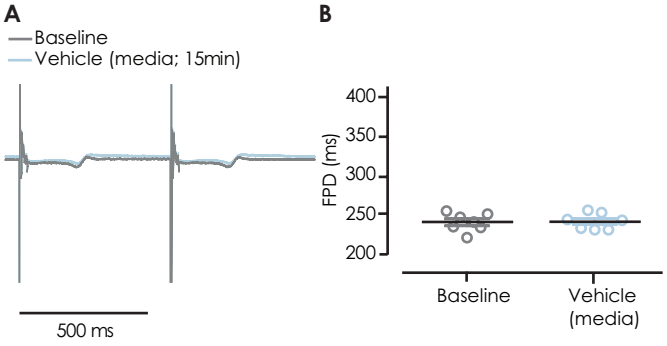

Figure 2: A) Representative EFP traces shown before (baseline) and after vehicle treatment (light blue). **B)** Quantification of the FPD before (baseline) and after vehicle application. There is no statistical difference between the two groups.

Exposure (15 minutes) to 30 µM and 100 µM lidocaine, resulted in 8 ± 1% and 15 ± 2% reduction in the estimated CV, respectively. Figure 3 shows the prolongation of the FPD upon lidocaine exposure (30 µM: 242 ± 4 ms vs. 303 ± 9 ms, n = 8, p < 0.005, paired t-test; 100 µM: 240 ± 4 ms vs. 348 ± 12 ms, n = 7, p < 0.005, paired t-test).

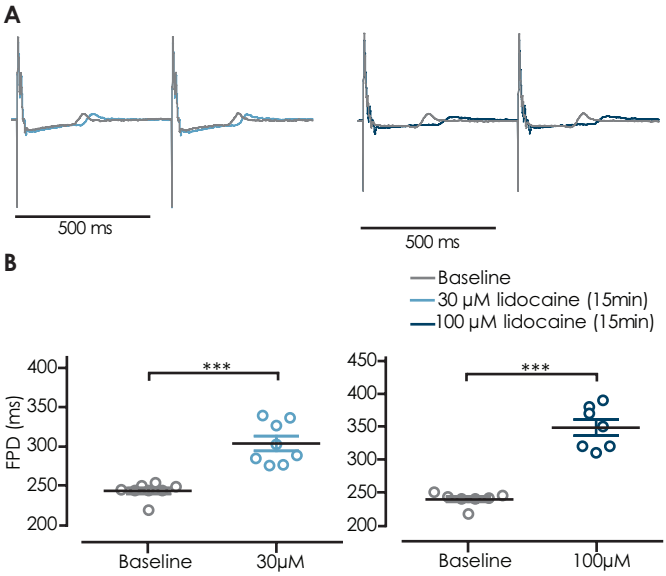

Figure 3: A) Representative EFP traces shown before (baseline) and after 30 µM (left) or 100 µM (right)lidocaine exposure. **B)** Quantification of the FPD before (baseline) and after 30 µM (left) or 100 µM (right) lidocaine exposure.

In summary, CV is related to how fast the membrane depolarizes and sodium channel blockers (like lidocaine) can reduce CV. Decreasing CV is often used to terminate arrhythmias caused by re-entry circuits. Therefore, the establishment of a method to estimate compound effect on conduction velocity with CardioExcyte 96 is an important aspect of the study of arrhythmogenesis, especially where it involves arrhythmias based on re-entry[6].

References

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Methods

Cells

We thank NEXEL Co., Ltd for providing the cells and the culture media. Cardiosight®-S were handled according to the manfacturer's guide provided by Nexel.

EFP measurements

EFP measurements were conducted according to Nanion's standard procedures for the CardioExcyte 96. Cardiosight®-S were plated onto NSP-96 Stim plates. After 7 days in culture the cardiomyocytes were electrically paced at 1.7 Hz with 1 ms pulse duration. After one hour under electrical pacing, vehicle or 30 µM and 100 µM lidocaine were added to the cardiomyocytes. EFP signals were recorded for one hour after compound addition.

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