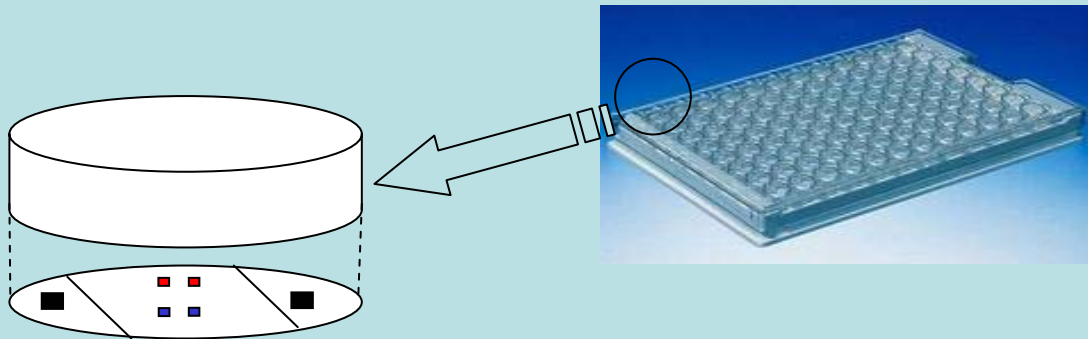




MED-QT Screen™

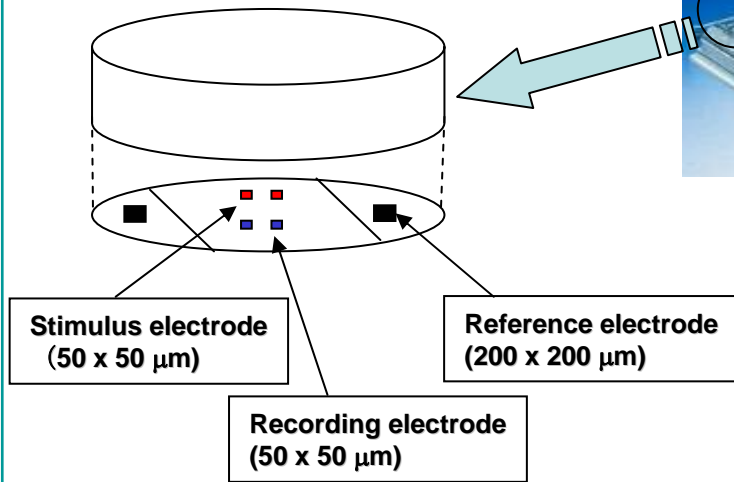
Automated Cardiac Electrophysiology for
Drug Profiling and Safety Testing



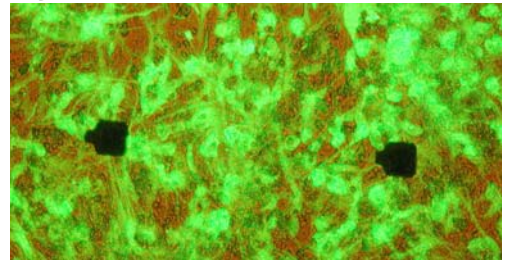
Features of The MED-QT Screen™ System

- Key technology is developed using reliable planar multi-electrode array technology by MED Systems (www.med64.com)
- Fully automated high throughput drug screening using cultured myocytes on a 96-well MED-QT Screen plate (with automated generation of concentration series via liquid handling component)
- Unlike assays based on transfected cells, the MED-QT Screen employs cardiac myocytes and directly measures the arrhythmogenic activity of tested compounds. The use of cardiac myocytes ensures that all cardiac ion channels contribute to the recorded signals in their native environment. It further offers a detection method for drugs that modify ion channel protein trafficking intracellularly. As such, QT Prolongation data obtained using the MED-QT Screen system reduces false positives and negatives and ensures that only the most effective and safest drugs enter clinical trials.
- Allows observation of long term effects of drugs on QT prolongation over days, weeks, or months
- Simpler, more cost effective screening methodology as compared to traditional methods
- Offers a potentially more successful screening method for the identification of drug candidates for discovery programs that are based on hERG prone targets.
- Spontaneous activity and Evoked response detection capacity (dose response measurements can be made at high concentration without concern of loss of spontaneous activity)
- Considered by the FDA ICH S7B Guideline a useful and complementary methodology for the nonclinical evaluation of the potential for delayed ventricular repolarization (QT Interval Prolongation)

Technology

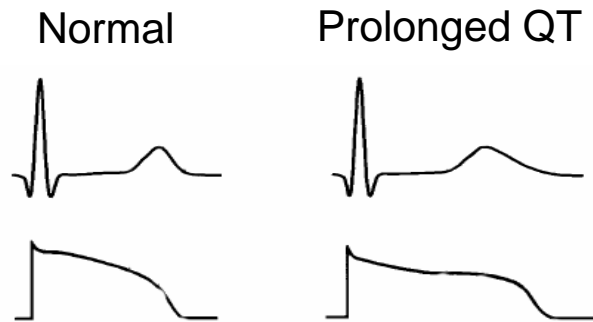


Myocyte cultured on the MED screen device



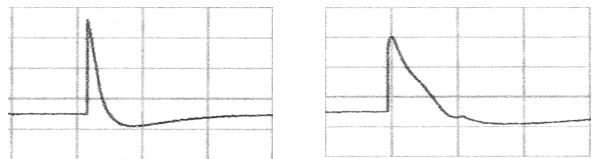
Recorded signal

■ ECG

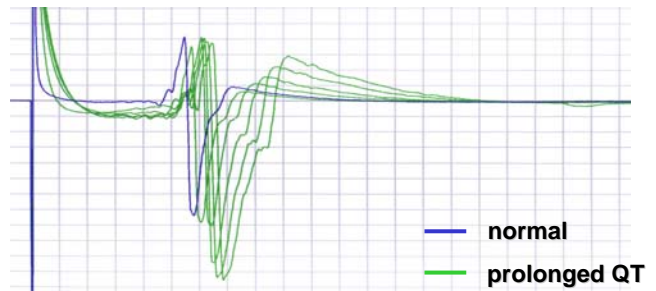


(Modified from Nakatani H, Nichiriyakushi, 2003, 121: 384-392)

■ Action potential by MED-Screen (Cultured myocyte)

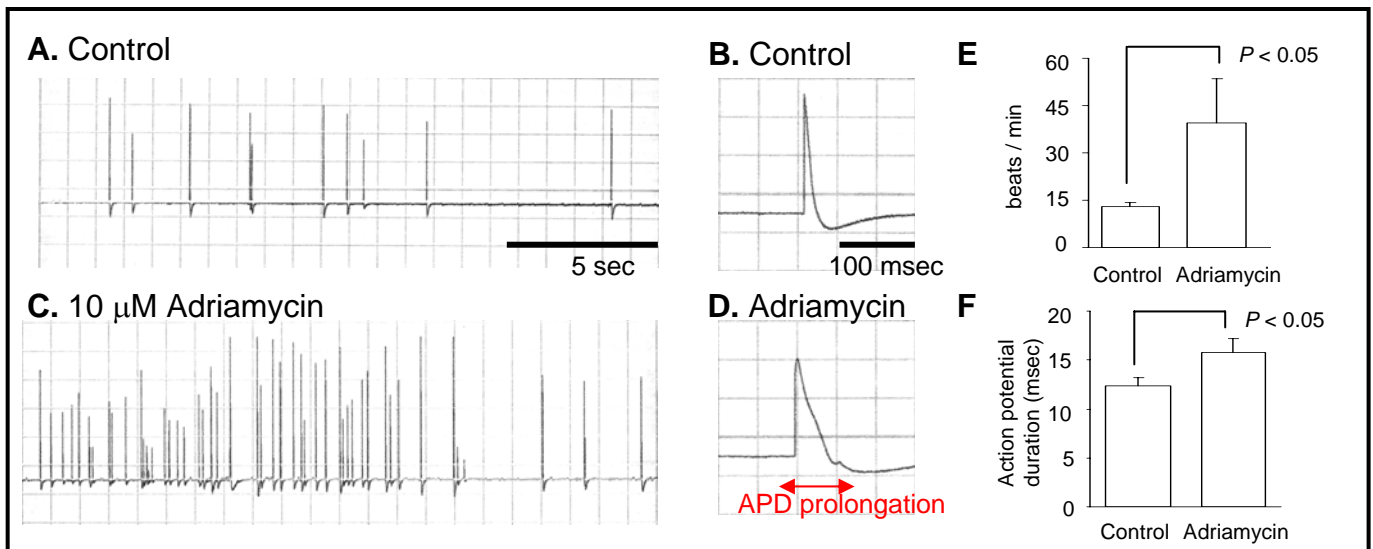


■ Action potential by MED screen (Evoked response)



Evaluation of Drug Effect Using MED-Screen Technology

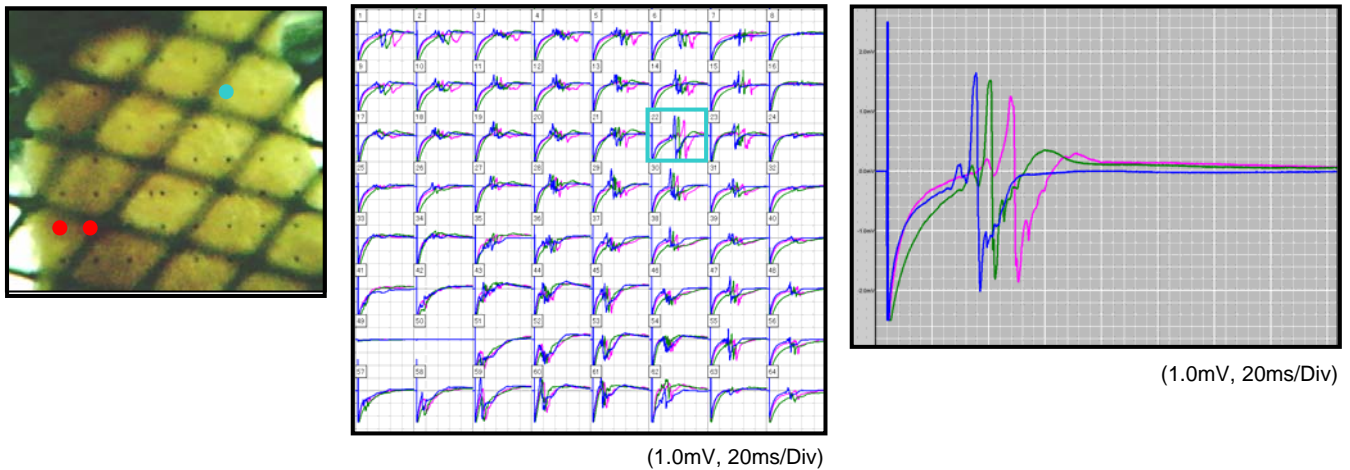
Evaluation of Drug Effect on Cultured Myocyte (Spontaneous Activity)



(A) shows spontaneous activities obtained from myocyte cultured on MED probe, while (B) shows the close-up view of one wave from them. In the presence of 10 μ M adriamycin, the frequency of spontaneous activity increased (C, E) and the duration of each spike is prolonged (D, F).

Courtesy of Drs. Nishida and Kurose, Grad. Sch. of Pharmaceutical Science, Kyushu University, Japan

Evaluation of Drug Effect on Acute Ventricular Slice (Evoked Action Potential)



[Left] Micrograph of adult rat left ventricular muscle slice (250 μ m thickness) on MED-P545A probe. (450 μ m inter-polar distance).

[Center] Pacing responses evoked by electric stimulation (100 μ A) to the two electrodes on MED probe (marked on red in the left picture) in the absence (blue), presence (pink) and wash out (green) of 100 μ M Quinidine.

[Right] Detailed view of signal obtained from ch 22. (marked in blue in the center figure). In the presence of 100 μ M Quinidine, latency and the duration of the action potential were prolonged, and the slope of the action potential became slow (response in pink). These effects were almost erased in the wash out phase (response in green).

Courtesy of Dr. Tsubone, Grad. Sch. of Agriculture and Life Sciences, University of Tokyo, Japan

Advantages

- Significantly enhanced throughput as compared to traditional methods
- Automated data analysis
- Automated generation of concentration series
- Automated liquid handling
- Stimulated Response capabilities
- Microplate screening will require significantly less substrate per screen
- 96-well format will offer significantly less hands on preparation and analysis time

Hands on time per run	5 min
Time per run	26 min
Data points per day	9216
Cost per data point	\$0.26 USD
Automated Analysis	YES
Stimulated Response	YES
Recordings per well	2

Throughput Analysis

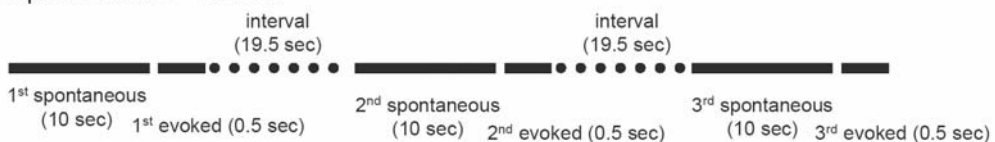
(Conditions)

- Each well has 2 recording electrodes
- 8 dose each drug
- 4 points (2 wells) each dose

1 plate (96 wells) can test 6 drugs

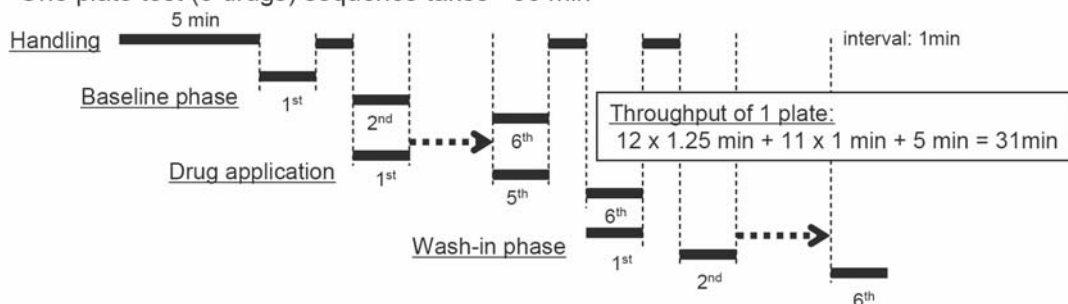
(Measuring sequence)

- Three sequential measurements are done in each baseline and wash-in phase
- One sequence takes ~75 sec



(Entire sequence)

- Measuring units can measure 16 wells (32 points) at same time (6 blocks)
- One plate test (3 drugs) sequence takes ~30 min



Specifications

MED screen device

- Number of well: 96
- Number of electrode in each well: 6 [Recording (2), Stimulating (2), Reference (2)]
- Size of recording/stimulating electrode: 50 x 50 μm
- Size of reference electrode: 200 x 200 μm
- Impedance of electrode: < 50 k Ω

Hardware

[Connecting unit]

Connecting stage: 1

[Amplifier unit]

Number of channel: 32 (recording/stimulating)
(recording amplifier)

- Input impedance: > 100 M Ω
- Amplification: x1000 (60dB)
- Internal noise: < 4 mV

(stimulus amplifier)

- Output: constant current
- Max output current: 2 mAp

[Acquisition unit]

A/D, D/A board: 1 (National Instrument, PCI-6071E)
Workstation PC, LCD monitor

Software

- Number of simultaneous recording: 96
- Type of recording signal: Spontaneous activities or/and Evoked response
- Analyses: Latency from stimulus
 - Duration of action potential
 - Amplitude of action potential
 - Frequency of burst

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