The 23rd Korean MEMS Conference

제23회 한국 MEMS 학술대회

2021.04.07(수) ~ 04.09(금), 부여 롯데리조트

| 논문원고접수 |

2020년 12월 14일(월) ~ 2021년 1월 13일(수)

| 논문심사결과 통보일 |

2021년 2월 17일(수)까지 홈페이지 (http://www.micronanos.org)에 공지 및 책임저자에게 이메일로 통보

| 초록 및 논문접수처 |

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| 논문범위 |

1. Materials, Fabrication, Packaging and Simulation Technologies
2. Micro/Nanofluidics
3. Bio/Medical Micro/Nano Devices
4. Physical and Mechanical Micro/Nano Sensors and Systems
5. Chemical and Environmental Sensors
6. RF/Optical Devices
7. Micro/Nano Energy and Power Devices
8. Soft, Flexible and Printed Devices

주최 : (사)마이크로나노시스템학회 (E-mail : master@micronanos.org, 전화 : 02-749-6482)

논문 No.	Journal Title	First Author	Corresponding Author	Presenting Author	Organization
FP-3-12	Improving the Maturity of the Cardiomyocytes using Diaphragm-based Mechanical Stimulation	Abdullah-Bin Siddique	이동원	Abdullah-Bin Siddique	전남대학교
FP-3-13	형광 이미징을 위한 초박형 고속 오프셋 어레이드 카메라	김현경	정기훈	김현경	한국과학기술원
FP-3-14	nanoFET 바이오센서의 동작원리 설명 및 가짜 신호 해석	강혜림	이국녕	강혜림	한국전자기술연구원
FP-3-15	Analysis of Bacterial Inoculum Effect by using Microscopic imaging in micropatterned biochip	황정호	최정일	최정일	국민대학교
FP-3-16	세포 소기관 유래에 따른 엑소좀 모사 나노소포의 다양성	이현진	박재성	이현진	포항공과대학교
FP-3-17	3차원 스페로이드의 경제적 생산을 위한 액적 기반 미세유체시스템 개발	이재훈	김현수	이재훈	한국기계연구원
FP-3-18	Fluidic Urea Biosensor Based on Effective Enzyme Immobilization	김지영	박민	김지영	한림대학교
FP-3-19	순차적 이온 농도 분극 현상을 이용한 종이접기 기반 혈청 농축기 Paper-based	이승민	이정훈	이승민	고려대학교
FP-3-20	다양한 신경 전극 디자인 설계를 통한 신경 자극 성능 검증	최원석	김진석	최원석	한국과학기술연구원
FP-3-21	Double-clip Neural Interface Using Shape Memory Polymer	조영준	이상훈	조영준	대구경북과학기술원
FP-3-22	Ultrasound-induced Heater based on AgNW-PDMS Composite Membrane	김우혁	박진수	김우혁	전남대학교
FP-3-23	엑소좀 분리를 위한 ATPS의 적용 종이칩 (Exosome isolation paper device based on Aqueous two-phase system (ATPS))	김진환	이정훈	김진환	광운대학교
FP-3-24	Microfluidic Chips with Electrical Stimulation Controller for Mechanism Research of Intervertebral Disc Degeneration	김안기	최혁	김안기	고려대학교 의생명연구센터 (고대구로병원)
FP-3-25	Surface-Enhanced Infrared Spectroscopy Based on Aluminum Metamaterial Absorber with nanogap	김민균	정주연	김민균	한국기계연구원
FP-3-26	Temperature Effects on Electro-Mechano-Physiology of NRVM Measured by a Dual-Function Biosensor	푸자	이동원	푸자	전남대학교
FP-3-27	Passive flow-rate regulating devices with output controllability depending on the flexible membrane thickness	남미송	허윤정	남미송	경희대학교
FP-3-28	Real-Time 3D Ultrasound Imaging with Trench-Insulated 2D Capacitive Micromachined Ultrasound Transducers	김혜연	이병철	김혜연	한국과학기술연구원
FP-3-29	의료용으로 적용 가능한 MEMS 열식 유연 유량센서의 제작과 평가	조명옥	임시형	장우진	국민대학교
FP-3-30	Multi-point Partial Pressure of Oxygen (pO2) Sensing Needle for Minimally-invasive Monitoring of Tumor Micro-environment	서보경	박인규	서보경	한국과학기술원
FP-3-31	금속 박막을 증착한 AAO wafer와 압전소자를 활용한 미세입자 분무장치 제작	김동준	이병철	김동준	한국과학기술연구원
FP-3-32	Continuous preparation of Bicelles Using Hydrodynamic Focusing Method and Analysis of Bicelle to Vesicle Transition	최성학	정호섭	최성학	서울대학교

Poster Session 4 (FP-4)

4월 9일 금요일
13:00~14:10

논문 No.	Journal Title	First Author	Corresponding Author	Presenting Author	Organization
FP-4-01	3차원 교류 전기 삼투 유동의 가시화	윤세혁	김성재	윤세혁	서울대학교
FP-4-02	표면전도 증진에 의한 아연 이온 전지 전극에서의 수지상 성장 억제	서주원	김성재	서주원	서울대학교
FP-4-03	다양한 세포 포획 압력에서 노화의 정도를 구분하기 위한 전기화학 임피던스 분광기	김원효	박양규	김원효	한국전자기술연구원
FP-4-04	이온 선택적 투과막 내 지지층에 따른 전기대류적 와류 고정에 대한 효과	서명진	김성재	서명진	서울대학교
FP-4-05	이온 선택성 막 근처에서 전기적 와류 불안정에 대한 이온 선택성 구조물의 이론적 분석	이도근	김성재	이도근	서울대학교

Temperature Effects on Electro-Mechano-Physiology of NRVM Measured by a Dual-Function Biosensor

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이중 기능 바이오 센서로 측정 된 NRVM 의 전기-기계 생리학에 대한 온도 영향

[1]Pooja Kanade, [1]Nomin Erdene Oyunbaatar, [1,2] 이동원*,

[1] 전남대학교 기계공학과, [2] 전남대학교 차세대센서연구개발센터

Abstract

Cardiomyocytes are being frequently used to analyze their response to various drugs during the preclinical phase. However, temperature effects, including hypothermic conditions, on the electrophysiology and mechanical response have not been studied simultaneously till date. In this study, we fabricated a novel dual-function biosensor that can measure both these responses of cardiomyocytes synchronously in a non-invasive manner and at the tissue level. Our biosensor was capable of detecting and measuring minute differences in field potential and contraction force on lowering the well-plate temperature. Field potential duration and beating duration started increasing on lowering temperature, and significant change was observed at 28 ºC. This shows that our biosensor was accurately able to predict heart parameters related to hypothermia.

Keywords: ***Cardiomyocytes (심근세포), Cantilever (캔틸레버), Microelectrode array ((미세 전극 배열), Temperature(온도), Hypothermia(저체온증)***

1. Introduction

Cardiomyocytes have been regularly used to investigate their underlying mechanisms pertaining to electrophysiology and contractility to screen their responses to various drugs and nanoparticles [1]. Studies have also been done to determine the effect of hypothermia (that is, temperatures < 28 ºC) on in-vitro cultured animal and human-induced stem cells [2-3]. Action potential duration (APD) increases on reducing temperature, as cardiomyocytes experience stress.

However, along with electrophysiological readouts, mechanical readouts also need to be undertaken, so that a broader understanding of the entire electro-mechano-physiological activity can be formed.

In this study, we undertook the objective of studying the simultaneous response of contraction force and extracellular field potential and how the cardiomyocytes responded to lowering temperature. The device was a miniature polymer-based cantilever, patterned with Cr/Au microelectrodes on the top. Neonatal rats' ventricular myocytes (NRVM) were cultured on this biosensor and simultaneous measurements were done by lowering temperature in a step-wise manner.

2. Methods and Materials

2.1 Working Principle of the Device

This dual-function biosensor simultaneously measures electrophysiology as well contractile response of cardiomyocytes, both of which are essential to understand cardiotoxicity in-depth. Contractile response is measured by fabricating an SU-8 based polymer cantilever. Thickness of the cantilever is kept low to enhance sensitivity. Upon culturing cardiomyocytes on the cantilever, measurement of the corresponding cantilever deflection upon their contraction and relaxation give the estimate of the amount of contraction force exerted by the cardiac tissue. Furthermore, microelectrodes made of Cr/Au are patterned on top of the cantilever that simultaneously measure field potential of the cardiomyocytes. 6 nos. of MEAs have been placed each on (1) free end of cantilever, (2) fixed end of cantilever and (3) on the device body, so that overall field potential trend is understood. Figure 1(a) shows the schematic of the proposed device, and figure 1(b) shows working principle of measurement of contraction force.

2.2 Experimental Details

Field potential was measured with the help of fabricated MEAs using a 64-channel amplifier (Intan Technologies RHD2164) connected to the Intan acquisition system (RHD2000). Sampling rate was kept at 15 kHz and the bandwidth of recorded measurement was 0.1 Hz – 5 kHz. For measurement of contraction force, a laser vibrometer (Polytec GmbH) based measurement setup was used. The laser vibrometer, that measures displacement in nanoscale, is placed vertically facing a home-made tabletop incubator, in which the cell cultured sample is placed for drug toxicity screening. Atmospheric temperature in the incubator is controlled at 37 ºC and CO_2 level at 5%.

Temperature of the well-plate was initially maintained at 37 ºC, after which it was lowered in steps of 3ºC, up to 22 ºC. The dual-

function biosensor measured both

3. Results and Discussion

Once the device was fabricated and prepared for cell culture, NRVM were seeded on it, as shown in figure 2(a). Cardiomyocytes were distributed uniformly throughout the cantilever. Our fabricated device is capable of accurately measuring field potential as well as contraction force in the form of cantilever displacement, as can be seen from figure 2(b).

Figure 3 shows the effect of lowering temperature on field potential. The field potential duration is increasing as the repolarization peak shifts towards the right side. Since the action potential duration increases at lower temperature, increase in the corresponding field potential is expected. Figure 4 shows how beating duration increases with lowering of temperature. Beating duration increases at 34 ºC and 31 ºC, however significant change occurs from 28 ºC. This can be attributed to the hypothermic conditions developed in cardiomyocytes. Contraction force showed no significant change.

From this study, we have proven our device capability to detect minute responses of cardiomyocytes with respect to changes in atmospheric conditions.

Acknowledgments

This study was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No.2017R1E1A1A01074550).

References

1. P. Kanade, N. Oyunbaatar, D. Lee, Polymer-Based Functional Cantilevers Integrated with Interdigitated Electrode Arrays—A Novel Platform for Cardiac Sensing, *Micromachines* ***11***, 450 (Apr. 2020).
2. T. Kiyosue, M. Arita, H. Muramatsu, A. J. Spindler, D. Noble, Ionic Mechanisms Of Action Potential Prolongation At Low Temperature In Guinea-Pig Ventricular Myocytes, *Journal of Physiology* ***468***, 85-106 (1993).
3. Y. Fu, G. Zhang, X. Hao, C. Wu, Z. Chai, S. Wang, Temperature Dependence and Thermodynamic Properties of Ca21 Sparks in Rat Cardiomyocytes, *Biophysical Journal* ***89***, 2533 (Oct. 2005).

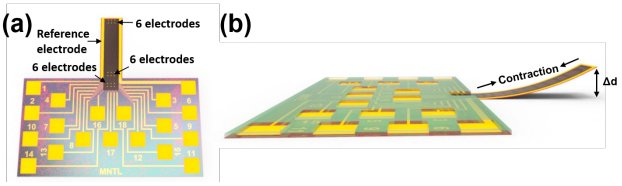

Fig. 1. (a) Schematic of the proposed dual-function biosensor denoting positions of the microelectrodes on the cantilever. Diameter of MEAs = 50 µm and pitch = 200 µm. Dimensions of cantilever are 6 mm x 2 mm, (b) working principle of measurement of contraction force by cantilever displacement.

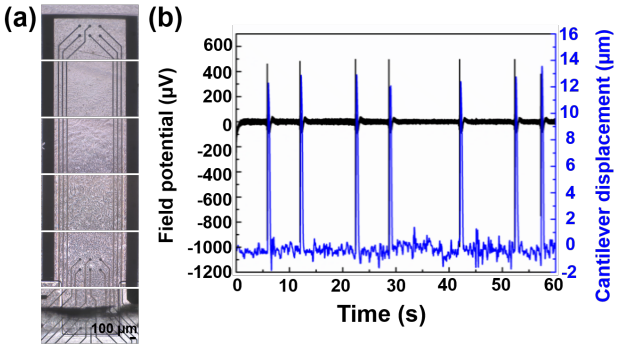

Fig. 2. (a) Optical image of the cantilever in cell culture medium, (b) simultaneous measurement of field potential and contraction force from the biosensor.

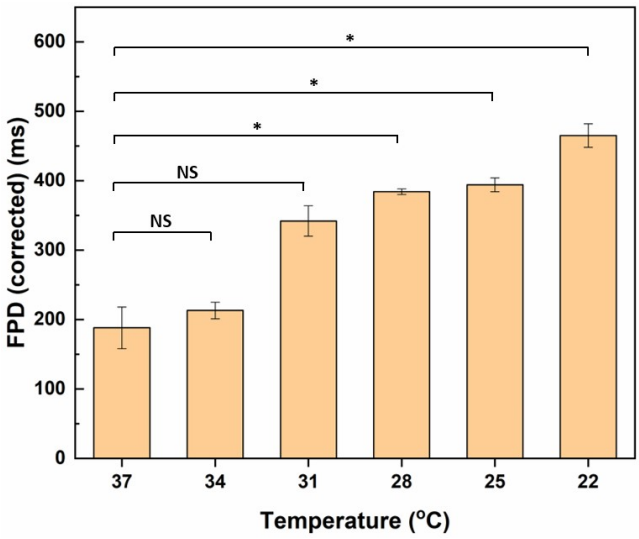

Fig. 3. Field potential duration (corrected using Fredricia's formula) with lowering temperature. n=3, * denotes P < 0.05.

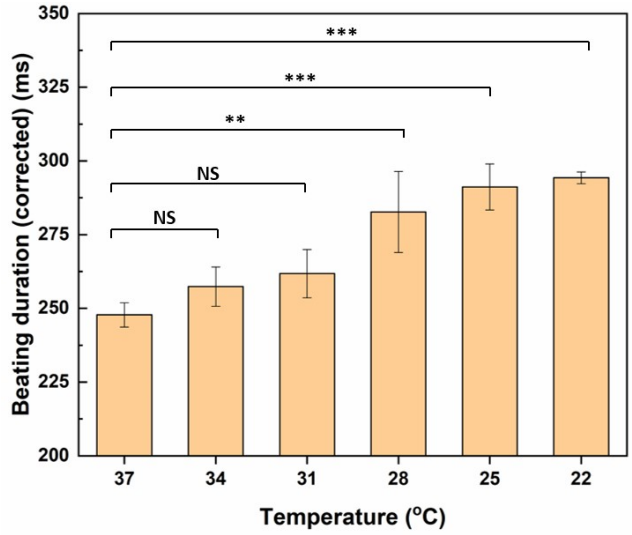

Fig. 4. Beating duration (corrected using Fredricia's formula) with lowering temperature. Analysis conducted using one-way ANOVA Tukey's test. n=3, ** denotes P < 0.005, *** denotes P < 0.0005.

FP-3-26

2021, 제23회 한국 MEMS 학술대회
(The 23rd Korean MEMS Conference), 2021년 4월 7일(수) ~ 9일(금)

The Society of Micro and Nano Systems

전남대학교 CHONNAM NATIONAL UNIVERSITY

MEMS & Nanotechnology Laboratory MNTL

Temperature Effects on Electro-Mechano-Physiology of NRVM Measured by a Dual-Function Biosensor

이중 기능 바이오 센서로 측정 된 NRVM의 전기-기계 생리학에 대한 온도 영향

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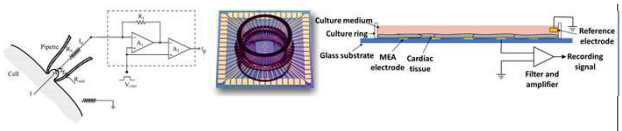
ABSTRACT

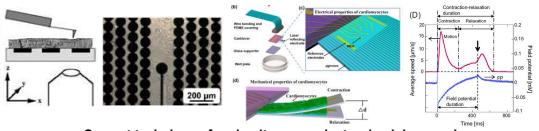
Cardiomyocytes are being frequently used to analyze their response to various drugs during the preclinical phase. However, temperature effects, including hypothermic conditions, on the electrophysiology and mechanical response have not been studied simultaneously till date. In this study, we fabricated a novel dual-function biosensor that can measure both these responses of cardiomyocytes synchronously in a non-invasive manner and at the tissue level. Our biosensor was capable of detecting and measuring minute differences in field potential and contraction force on lowering the well-plate temperature. Field potential duration and beating duration started increasing on lowering temperature, and significant change was observed at 28 °C. This shows that our biosensor was accurately able to predict heart parameters related to hypothermia.

◆Keywords : Cardiomyocytes (심근세포), Cantilever (캔틸레버), Microelectrode array ((미세 전극 배열), Temperature(온도), Hypothermia(저체온증)

INTRODUCTION



Current techniques for electrophysiology measurement



Current techniques for simultaneous electrophysiology and contraction force measurement

These techniques measure only the electrophysiology of cardiomyocytes and not mechanophysiology

Invasive, low-throughput and elaborate techniques have been developed so far

Motivation

- Cardiac cells show chronotropy but no significant inotropy in response to β-adrenoceptor agonist such as isoproterenol and nifedipine; i.e. several drugs only show changes in contraction force but not electrophysiology of cardiac cells, and vice versa.
- Simultaneous electrophysiology and mechanical recordings not analyzed extensively till date
- Hence, there is a need of an integrated platform to measure simultaneous electrophysiological and mechanical response.

Objective

- To develop a high throughput integrated cardiac sensing drug screening platform for simultaneous measurement of electrophysiological and mechanical properties of cardiomyocytes
- This dual function biosensing platform is to be realized using a cantilever-based non-invasive mechanical device that has microelectrodes patterned on it.

DEVICE CONCEPT

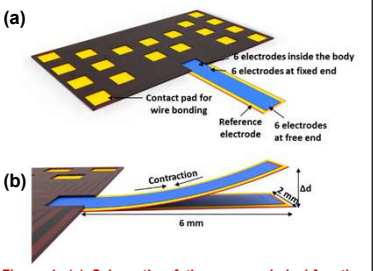


Figure 1. (a) Schematic of the proposed dual-function biosensor denoting positions of the microelectrodes on the cantilever. Diameter of MEAs = 50 μm and pitch = 200 μm, (b) working principle of measurement of contraction force by cantilever displacement.

DEVICE FABRICATION

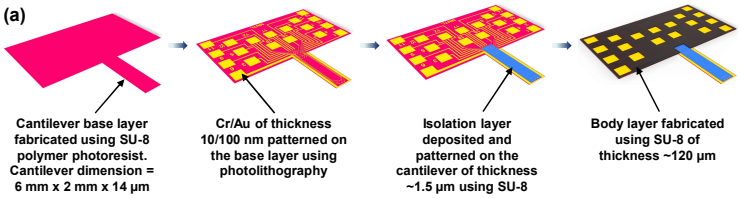


Figure 2. (a) Fabrication process flow of the proposed dual-function biosensor. The cantilever layer is deposited first using photolithography using a photosensitive polymer, then microelectrodes of Cr/Au, then isolation layer and, lastly, body layer of the device is fabricated, (b) optical image of the final dual-function biosensor showing positions of microelectrodes and reference electrode on the cantilever. Scale bar = 200 μm.

EXPERIMENTAL RESULTS

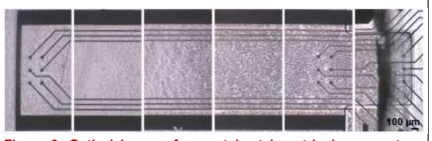


Figure 3. Optical image of neonatal rats' ventricular myocytes (NRVM) distributed on the entire cantilever.

- Shape of the extracellular field potential signal is similar in all electrodes of cantilever, including field potential duration – with a small propagation delay in each area.

EXPERIMENTAL RESULTS

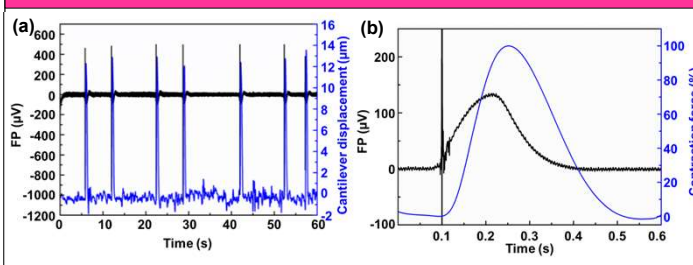


Figure 4. (a) Field potential and cantilever displacement measured simultaneously from the fabricated dual-function biosensor, (b) overlapped curve of field potential and contraction of one waveform.

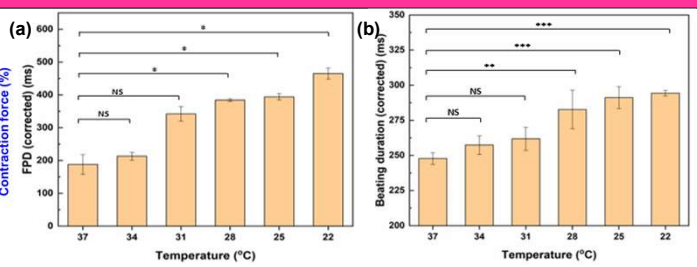


Figure 5. Drug-induced toxicity screening test using verapamil. (a) Field potential duration (corrected using Fredricia's formula) with lowering temperature. n=3, * denotes P < 0.05, (b) Beating duration (corrected using Fredricia's formula) with lowering temperature, n=3, ** denotes P < 0.005, *** denotes P < 0.0005.

- Since the action potential duration increases at lower temperature, increase in the corresponding field potential is expected.
- Increase in beating duration can be attributed to the hypothermic conditions developed in cardiomyocytes.

CONCLUSION

We have successfully demonstrated a high-throughput dual function biosensor that can simultaneously measure electrophysiology and mechanophysiology of cardiomyocytes. , We have proven our device capability to detect minute responses of cardiomyocytes with respect to changes in atmospheric conditions.

ACKNOWLEDGMENT

This study was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2017R1E1A1A01074550).

REFERENCE

[1] P. Kanade, N. Oyunbaatar, D. Lee, Polymer-Based Functional Cantilevers Integrated with Interdigitated Electrode Arrays—A Novel Platform for Cardiac Sensing, Micromachines 11, 450 (Apr. 2020).
[2] T. Kiyosue, M. Arita, H. Muramatsu, A. J. Spindler, D. Noble, Ionic Mechanisms Of Action Potential Prolongation At Low Temperature In Guinea-Pig Ventricular Myocytes, Journal of Physiology 468, 85-106 (1993).
[3] Y. Fu, G. Zhang, X. Hao, C. Wu, Z. Chai, S. Wang, Temperature Dependence and Thermodynamic Properties of Ca21 Sparks in Rat Cardiomyocytes, Biophysical Journal 89, 2533 (Oct. 2005).