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Piezoresistive sensor-integrated PDMS cantilever: A new class of device for measuring the drug-induced changes in the mechanical activity of cardiomyocytes

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ABSTRACT

Herein, we demonstrate in detail the fabrication and evaluation procedure of a piezoresistive sensor-integrated polydimethylsiloxane (PDMS) cantilever for measuring the drug-induced changes in the contraction force of cardiomyocytes. The proposed device consists of a glass body with metal patterns, a PDMS cantilever with microgrooves (μgrooves), and integrated piezoresistive sensor. Reliability of the piezoresistive sensor and connection wires was greatly improved by using a glass substrate with metal patterns. The longitudinally patterned μgrooves formed on the PDMS cantilever was optimized to maximize cantilever deformation. The mechanical deformation of the cantilever caused by the contraction force of cardiomyocytes is directly observed by using the integrated piezoresistive sensor, whereas the existing methods rely on the optical methods to measure the cantilever displacement. The contraction force is maximized between day eight and nine after seeding the cardiomyocytes onto the PDMS cantilever. After preliminary experiments, the strain sensor integrated μpatterned PDMS cantilever was subjected to measure the change in the contraction force of cardiomyocytes under different concentrations of cardiac drugs. The experimental results showed that the strain sensor integrated PDMS cantilever can effectively verify the changes in the mechanical output of the cardiomyocytes under the drug influence.

1. Introduction

The most important function of the heart is to pump the blood, supplying oxygen/nutrients to a human body by regular contraction and relaxation cycle of the working cardiomyocytes. When there is a problem in the regulation of contractility of cardiomyocytes a person may experience an abnormal heart rhythm. This often causes a serious situation to human health [1,2]. There are several reasons behind the abnormal heart functioning, among them preclinical drug use causes the high failure rates [3]. Hence, an accurate measurement and analysis of cardiac contractility is a key component for several pharmacological studies [4–12].

The mechanical activity of cardiomyocytes under the drug influence is usually carried out by measuring the contraction force of cardiomyocytes. In these studies, the isolated cardiomyocytes are placed onto biocompatible substrates and grown in-vitro at appropriate conditions. During the culture period the cardiomyocytes rearrange their myofibrillar and start to beat spontaneously again [13–16]. Over the years several techniques have been proposed to measure the contraction force of cardiomyocytes [17–24]. Of these techniques, much attention has been paid to polymeric microposts or cantilevers that directly measure the physiological behaviours of cardiomyocytes. The micropost array (μPA)/cantilever method measures the contraction force of cardiomyocytes through the mechanical deformation of cylindrical elastomer/polymeric cantilever. Although, these technologies used extensively to measure the contraction force of cardiomyocytes [25], it has several drawbacks such as it need an external optical device to measure the displacement of the structures, inability to work within a microarray format, the periodical alignment and calibration of a laser source is really a time consuming process when we employ the array of cantilevers [26,27].

In order, to overcome the all the practical difficulties of the methods, herein we present a novel technique for measuring

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the contractile force of isolated cardiomyocytes. The proposed cantilever device can measures the cantilever mechanical deformation/contraction force of cardiomyocytes electrically and it does not rely on any optical methods. To measure the mechanical deformation electrically, we bring in the innovative concept of using the strain induced by the mechanical deformations of the cantilever. The bending of the cantilever caused by the contraction force of cardiomyocytes can be measured effectively and effortlessly by monitoring the change in electrical signal passing through the strain senor. The cantilever is made by a biocompatible, flexible and optically transparent-polydimethylsiloxane (PDMS) material. To maximize the contraction force of cardiomyocytes and to improve the mechanical deformation of the cantilever we introduced the three-dimensional (3D) microgroove patterns on the surface of PDMS cantilever. The strain sensor integrated onto the PDMS cantilever through the conventional photolithography and metal etching processes. Further, thermal stability and electrical reliability of the μpatterned PDMS cantilever were greatly improved through the chemical attachment of PDMS cantilever with the metal wire deposited glass electrode.

Finally, the fabricated strain sensor integrated PDMS cantilever was used to measure the drug induced changes in the mechanical activity of cardiomyocytes. For cell seeding experiment, the heart was aseptically isolated from a Sprague-Dawley rat on day 3. The separated ventricles are washed by using ADS buffer solution, then single cardiomyocytes were acquired through enzyme solution and pre-plating. The acquired cardiomyocytes are then seeded onto the strain sensor integrated μpatterned PDMS cantilever. The change in contraction force of cardiomyocytes in response to the different concentrations of two drugs (Isoproterenol and Verapamil) was measured through cantilever bending displacement. The experimental results clearly demonstrate the effect of these drugs on the mechanical activity of cardiomyocytes. Hence we sincerely anticipated that the μpatterned PDMS cantilever arrays integrated with a strain sensor opens up a great opportunity to establish the new class of device for efficient and effective measurement of the drug induced changes in the mechanical activity of cardiomyocytes under the drug influence.

2. Material and methods

2.1. Design and fabrication of PDMS cantilevers

Due to the difference in thermal expansion coefficients between the metal wires and soft PDMS substrate thermal stress often exists during the metal deposition process which leads to the cracks and wrinkles on thin metal wires. To overcome these intrinsic problems, several approaches have been investigated. For example, Chou et al. demonstrated the stable deposition and metal patterning layers on PDMS substrate. In this method the parylene C which has high young's modulus (2.76 GPa) and thermal expansion coefficient ($3.5 \times 10^{-5}\ K^{-1}$) has been deposited on PDMS substrate. Baek et al. proposes another fabrication process to increase the PDMS surface roughness through reactive ion etching (RIE) method [28,29]. However, these methods have associated with some disadvantages, such as changes in the properties of the fabricated PDMS devices and breaking of wires owing to the high tension/compression in the PDMS during the fabrication processes/long-term operation. Fig. 1(a) shows the optical images of the PDMS cantilever, fabricated by using the existing fabrication processes. The fabricated PDMS cantilever exhibits the cracks and wrinkles caused by the thermal stress. In particular, the cracks cause the wire breakdown and the wrinkles increase the surface roughness of the device (Ra = 163.11 nm), thereby reducing the reliability and stability of the device electrical resistance.

To conquer this negative aspect of the fabricated device, we proposed the novel structure to realize the crack-free metal patterns and subsequent resistance stability at the PDMS substrate. The surface roughness of the PDMS substrate is greatly improved by employing a glass substrate. As shown in Fig. 1(b) the proposed structure consists of two parts (i) strain sensor-integrated PDMS cantilever and (ii) thin metal wires deposited glass substrate. Finally, the glass substrate was chemically bonded with the strain sensor-integrated PDMS cantilever, through which the durability and resistance reliability of the device is dramatically improved.

The detailed fabrication process of strain sensor-integrated PDMS cantilever is schematically illustrated in Fig. 2. The μpatterned PDMS cantilever is prepared by using general MEMS process such as etching and lift-off. In this fabrication process first, the photoresist film patterned on Si wafer through the conventional

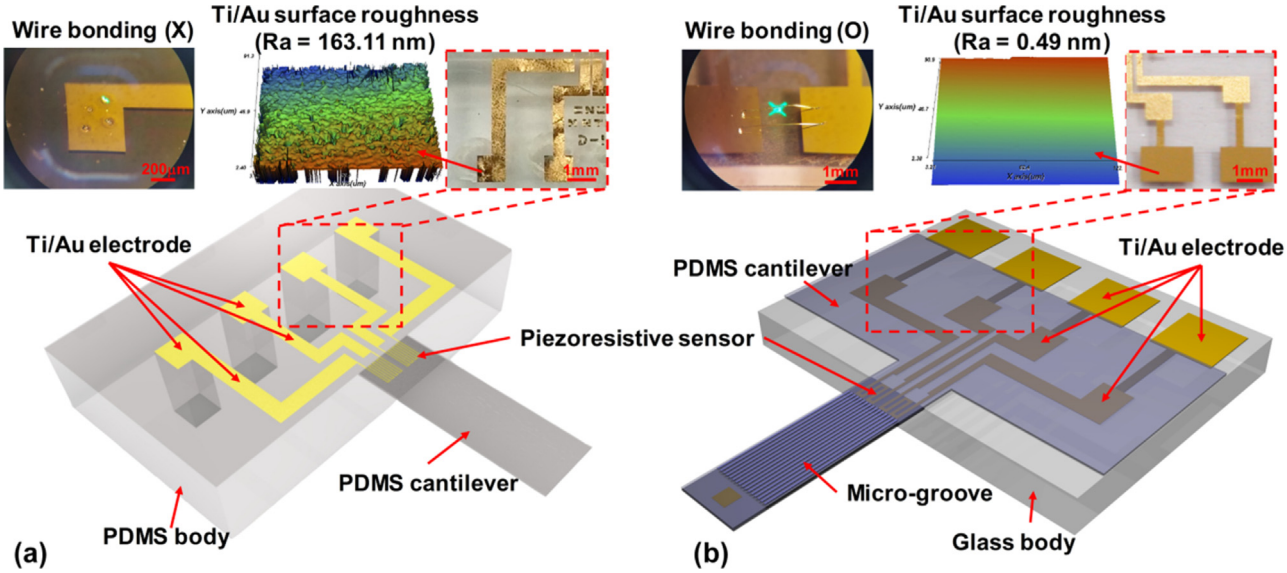

Fig. 1. Schematics of PDMS cantilevers for drug toxicity screening application. (a) Strain sensor-integrated μpatterned PDMS cantilever. (b) Advanced PDMS cantilever with improved electrical reliability.