様　式　C－１９、F－１９－１、Z－１９　（共通）

科研費 KAKENHI

科学研究費助成事業　　研究成果報告書

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研究課題名（和文）呼吸器系のその場連続監視に向けた生分解性埋込み型流量センサ

研究課題名（英文）Biodegradable implantable flow sensor for on-site continuous monitoring of respiratory system

研究代表者

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交付決定額（研究期間全体）：（直接経費）　　2,400,000円

研究成果の概要（和文）：肺癌や慢性閉塞性肺疾患(COPD)などの呼吸器疾患は世界中で主要な死因となっている。さらに、最近拡大している新型コロナウイルスの感染がその状況を悪化させている。これらの感染症の治療法は現在存在しないが、リスクの高い患者の早期発見と継続的なモニタリングにより、その進行を遅らせることができると考えている。本研究では微小電気機械システム（MEMS）技術を用いて小型熱式流量センサを作製し、人工呼吸器ならびに動物実験を通して作製したセンサを用いて呼吸の計測・モニタリングを原理実証した。その後、同様な仕組みを通して、生分解性材料を用いて新規流量センサを作製した。

研究成果の学術的意義や社会的意義
本研究ではMEMS流量センサを用いて呼吸の計測・モニタリングが可能であることを実証した。また、生分解性材料を用いたMEMS流量センサの作製技術も確立した。本センサを用いることで呼吸モニタリングが可能にし、センサが動作期間を超えた後に自然に消え、デバイスを回収するための手術が不要になる。

研究成果の概要（英文）：Respiratory diseases such as lung cancer and chronic obstructive pulmonary disease (COPD) have become major causes of death worldwide. Furthermore, the recent outbreak of novel coronavirus infection (COVID-19) has exacerbated the situation. Although there are currently no specific treatments for these infectious diseases, it is believed that early detection and continuous monitoring of high-risk patients can delay their progression. In this study, we developed a miniaturized thermal-based flow sensor using micro-electro mechanical systems (MEMS) technology. We then demonstrated its capability for respiratory measurement and monitoring through model experiments using an artificial ventilator and animal experiments using rat. Subsequently, we fabricated a biodegradable flow sensor employing a similar mechanism.

研究分野：ナノマイクロシステム

キーワード：MEMS　流量センサ　生分解性　埋込み型　フレキシブル

１．研究開始当初の背景

Respiratory diseases, including lung cancer and chronic obstructive pulmonary disease (COPD), are of the leading causes of death worldwide (World Health Organization (WHO) Report 2019). They are caused by inhalation of air pollutants, including cigarette, industrial and vehicle smoke, which have been on the rise due to industrialization. The emergence of COVID-19 further worsen the situation. Currently, there is no cure to these deadly infections, but its progression can be delayed by early detection and continuous monitoring of high-risk patients. Non-invasive methods such as spirometry and x-ray are used to examine the patients. During spirometry, a tube is held into the mouth and the respiratory state is evaluated by a physical quantity: flow rate. Meanwhile, the x-ray shows the image of the entire lung to identify the location and size of the tumor. However, both single-point examinations require periodical visits to the hospital, which is costly and inefficient.

２．研究の目的

For long term monitoring of the respiratory health, continuous monitoring of the pulmonary system is demanded. There are 3 important components to realize such a system: power source, electronics and sensor. Among these components, this study aims to develop a biodegradable flexible flow sensor to be implanted in human respiratory tract. The implantable device with a similar flexibility as human respiratory tract is more preferable than the wearable counterpart to reduce discomfort in the daily life. Furthermore, in-vivo measurement could provide more in-depth analysis of the condition of the pulmonary system. For such an implantable device, the device retrieval often requires a surgery. Biodegradability is the key to eliminate the retrieval procedure of post-operational devices. A new microfabrication process platform will be developed to realize the proposed biodegradable flexible system. The system is designed to evaluate the airflow and monitor it continuously.

３．研究の方法

① MEMS flow sensor for respiration measurement

Various methods have been proposed for respiration monitoring. The first step of this study involves the fabrication of a micro-electro mechanical systems (MEMS) flow sensor for quantitative respiration measurement. The thermal sensing mechanism was utilized due to its excellent performance. The absence of resonating structure also gives the mechanism a higher degree of reliability. For the proof of concept, a non-biodegradable flexible MEMS flow sensor was fabricated. A thermal flow sensing structure was patterned on a polyimide (PI) film and the film sensor was packaged inside a tube for defining the airflow region. The sensing structure was formed by thin film Au metallization. The structure consists of 3 thin film resistors, one at the middle working as a heater and the other 2 at its opposing sides working as temperature sensors.

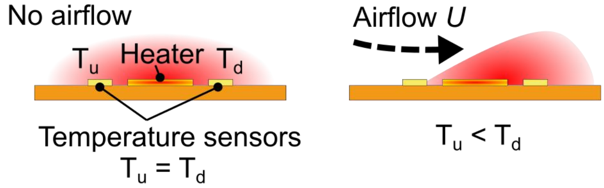

Fig. 1: Calorimetry airflow rate measurement principle.

The airflow sensing works according to thermal calorimetry as illustrated in Fig. 1. The heater was

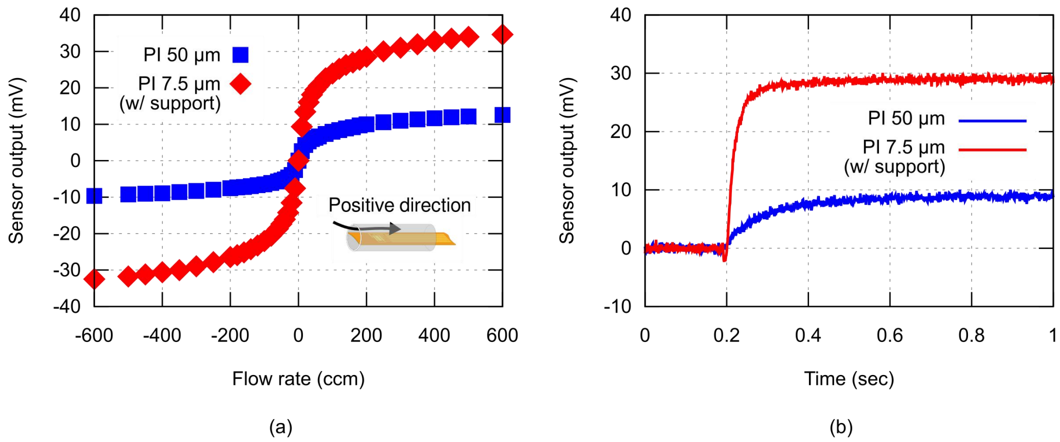

Fig. 2: Basic characteristics of the fabricated sensor with respect to (a) controlled airflow inputs and (b) step input of 300 ccm aiflow.

actuated through Joule heating and feedback controlled at a constant temperature. In the presence of the airflow, the heat generated by the heater is lost due to forced convection and the resistance of the heater suddenly drops. This sudden drop is detected by an integrating circuit and additional potential is accordingly supplied to maintain the heater temperature constant.

The airflow rate sensing was performed by the 2 temperature sensors placed in the upstream and downstream directions of the heater. The temperature sensors work in accordance to the temperature coefficient of resistance of thin film metallic resistors. When the surrounding temperature change, the resistance of thin film resistors follows. In the absence of the airflow, the heat generated by the heater is evenly distributed in both the upstream and downstream directions. As a result, there is no difference in the temperature readings of both the temperature sensors. In the presence of the airflow, the forced convection causes the temperature reading of the sensor at the upstream to drop, while the temperature reading of the sensor at the downstream rises. The airflow rate was determined from the difference of the readings of both the temperature sensors. Proof of concept evaluation was performed using both an artificial ventilator and animal experiment.

② Fabrication of biodegradable flow sensor

A MEMS thermal sensor with similar sensing structure with the above sensor was fabricated using entirely biodegradable materials. A water solvable flexible polyvinyl alcohol (PVA) sheet was utilized as the substrate in place of the PI film. Meanwhile, Mo was selected for the sensing structure metallization. The sensing structure patterning using standard MEMS process was established.

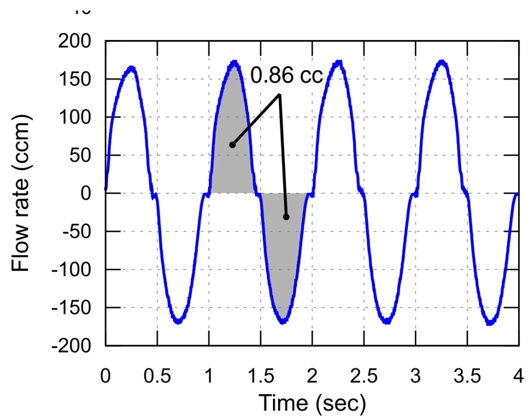

Fig. 3: Reciprocating airflow produced from an artificial ventilator.

4．研究成果

The fabricated MEMS airflow sensor was characterized with respect to a controlled input airflow. The measurement result for different sensing substrate thickness is shown in Fig. 2. The measurement result in Fig. 2 (a) was utilized as a calibration curve to convert the sensor output to the airflow in the following proof of concept experiments. From the response to the step airflow input shown in Fig. 2 (b), the response speed of the sensor was calculated from the required time to reach 90% of the steady response, which was up to 20.8 Hz. The first proof of concept experiment was performed using an artificial ventilator. The reciprocating airflow produced by the ventilator imitates the respiration airflow in living beings. The measurement result is shown in Fig. 3. The tidal volume of each wave was calculated by integrating the area under the airflow rate curve. Small mismatch of the tidal volume in both the direction showed an excellent sensor performance. Next, the fabricated sensor was utilized to measure the respiration of an experimental animal, namely rat. The obtained result is as shown in Fig. 4. The obtained tidal volume was within the range of typical values of rat of 0.6-2.0 cc. Meanwhile, the fabricated biodegradable flow sensing structure is depicted in Fig. 5. The sensor was completely dissolved in water within several days.

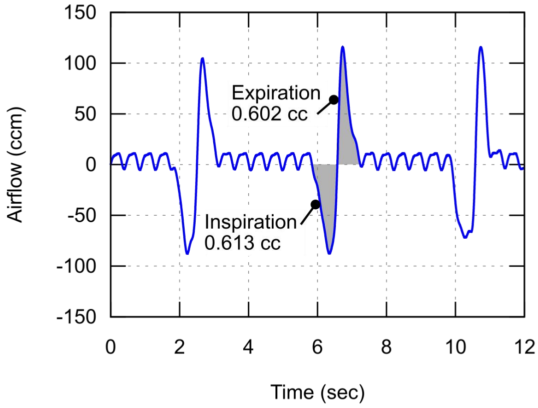

Fig. 4: Respiration airflow of a rat.

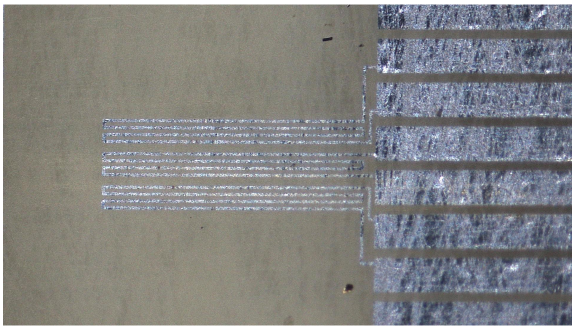
Fig. 5: Micrograph of the fabricated biodegradable flow sensor.

5．主な発表論文等

〔雑誌論文〕　計2件（うち査読付論文　1件／うち国際共著　0件／うちオープンアクセス　1件）

1．著者名 Muhammad Salman Al Farisi、Yang Wang、Yoshihiro Hasegawa、Miyoko Matsushima、Tsutomu Kawabe、Mitsuhiro Shikida	4．巻 23
2．論文標題 Facile In-Tube-Center Packaging of Flexible Airflow Rate Microsensor for Simultaneous Respiration and Heartbeat Measurement	5．発行年 2023年
3．雑誌名 IEEE Sensors Journal	6．最初と最後の頁 In press
掲載論文のDOI（デジタルオブジェクト識別子） 10.1109/JSEN.2023.3272310	査読の有無 有
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 －

1．著者名 Muhammad Salman Al Farisi、Yang Wang、Yoshihiro Hasegawa、Miyoko Matsushima、Tsutomu Kawabe、Mitsuhiro Shikida	4．巻 -
2．論文標題 Facile In-Tube-Center Packaging of Flexible Airflow Rate Microsensor for Simultaneous Respiration and Heartbeat Measurement	5．発行年 2023年
3．雑誌名 TechRxiv	6．最初と最後の頁 1-8
掲載論文のDOI（デジタルオブジェクト識別子） 10.36227/techrxiv.22720810	査読の有無 無
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〔学会発表〕　計1件（うち招待講演　0件／うち国際学会　1件）

1．発表者名 Muhammad Salman Al Farisi、Yang Wang、Yoshihiro Hasegawa、Miyoko Matsushima、Tsutomu Kawabe、Mitsuhiro Shikida
2．発表標題 In-tube-center packaging of flexible MEMS airflow-rate sensor and its sensitivity enhancement
3．学会等名 The 22nd International Conference on Solid-State Sensors, Actuators and Microsystems (Transducers 2023)（国際学会）
4．発表年 2023年

〔図書〕　計0件

〔産業財産権〕

〔その他〕

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6．研究組織

	氏名 （ローマ字氏名） （研究者番号）	所属研究機関・部局・職 （機関番号）	備考

7．科研費を使用して開催した国際研究集会

〔国際研究集会〕　計0件

８．本研究に関連して実施した国際共同研究の実施状況

共同研究相手国	相手方研究機関