International Journal of Gerontology 7 (2013) 147–151

Contents lists available at SciVerse ScienceDirect

International Journal of Gerontology

journal homepage: www.ijge-online.com

Original Article

Monitoring Apnea in the Elderly by an Electromechanical System with a Carbon Nanotube-based Sensor☆

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ARTICLE INFO

Article history:
Received 23 December 2011
Received in revised form
28 May 2012
Accepted 17 December 2012
Available online 28 February 2013

Keywords:
apnea,
breath sensor,
carbon nanotubes,
sensors

SUMMARY

Background: Breathing, a part of respiration, is one of the vital functions. Breathing disorders are common in the elderly. An effective breathing sensor for real-time detection of apnea is important in clinical critical care. We aimed to construct a real-time warning platform with a combination of carbon nanotubes (CNTs) and related nano-electromechanical system (NEMS) for elderly care.
Methods: Through a specific acid-treated procedure, multiwalled carbon nanotubes (MWCNTs) were immobilized on a thin silicon dioxide (SiO_2) film, coated on a heated silicon wafer. Techniques of photolithography and sputtering with chromium and gold were then implemented on the MWCNT film to develop micro-interdigitated electrodes as a base for the breathing sensor. The sensor was equipped with a programmed microchip processor to become a warning detector for abnormal human breathing, namely less than six breaths per minute. Elderly volunteers were enrolled for examining the effective sensitivity of this novel electromechanical device.
Results: There were 15 elderly volunteers (9 males and 6 females) tested in this experiment. The dynamic analyses of the MWCNT sensor to exhaled breath showed that it had characteristics of rapid response, high aspect ratio, small tip ratio, and high electrical conductivity. Responses of the MWCNT sensor to exhaled breath was recorded according to different performance parameters, i.e., strength, frequency, flow rate, and breath components. In this study, variable pattern-simulated tests showed that a MWCNT sensor combined with a processor could accurately evoke warning signals (100% of sensitivity rate), indicating its effectiveness and usefulness for detecting abnormal breathing rates, especially apnea.
Conclusion: Our results showed that a new device composed of an NEMS by combining an MWCNT sensor and complementary metal-oxide semiconductor (CMOS) circuits could be integrated to effectively detect apnea in the elderly. This novel device may improve the pattern of safe respiratory care for the elderly in the future.

1. Introduction

Breathing, a part of respiration reflecting various signs about physiological conditions, is a basic but vital function[1]. Aging and diseases result in disorders of human breathing and cardiopulmonary systems[2]. Therefore, the development of a smart device to detect breathing performance and the components of breath is significantly important for the comprehensive analysis of lung function, asthma detection, and diabetes mellitus[3–6]. Furthermore, health condition can also be reflected by this kind of device through delicately monitoring the physical characteristics of the exhaled breath, such as breath frequency and tidal volume, in order to improve the quality of medical care and treatment[1]. Therefore, developing a good sensor with high sensitivity, fast response, reproducible production, low cost and high reliability is an important issue in medical fields.

Although several different types of breath measurement have been used currently, there are still many defects and limited applications in clinical practice. Pressure sensors, which checks the pressure change induced by the exhaled gas, are widely used as respiratory monitors for intubated patients. A tube connecting the mouth or nose with a wind-tight system is necessary; otherwise, the pressure-sensitive element may be disturbed by ambient flow[7]. Body

☆ All contributing authors declare no conflicts of interest.

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1873-9598/$ – see front matter
http://dx.doi.org/10.1016/j.ijge.2013.01.004

shape sensors, which are popularly used for sleep apnea disorders, reflect the breath condition indirectly via a pressure change due to modification of the chest and abdomen; however, the discomfort caused by tying the sensor onto the body limits the application of this type of sensors[1]. Three other types of sensors (temperature sensor, sound sensor, and humidity sensor) through detecting the characteristics of the physical change during breathing, have also been reported[1,8–10]. However, weaknesses such as easy disturbance by ambient noise are commonly found, which limit its wide application.

With the advent of nanotechnology, research is underway to create new types of miniaturized sensors. Miniaturized sensors can lead to reduced weight, lower power consumption, and low cost. The discovery of carbon nanotubes (CNTs) has generated keen interest among researchers to develop CNT-based sensors for breath. CNTs are hexagonal networks of carbon atoms of approximately 1–10 nm diameter and 1–100 μm length[11]. They can essentially be thought of as a layer of graphite rolled-up into a cylinder, with a layer of single-wall carbon nanotubes (SWCNTs) or more multi-wall carbon nanotubes (MWCNTs). CNT networks have high carrier mobility in electronic field effect, with a high electromigration threshold, a high thermal conductivity, and exceptional mechanical properties[12]. Since the unique physical properties and potential in diverse range of applications, CNT sensors have been reported by a few authorized teams as breath sensors[1,13,14]. However, detailed structures and designs of applications with this kind of sensor in practice are still limited, especially for use in elderly people. Based on these aspects, in the present study we designed a testing platform with an MWCNT-based sensor through an integrated technology to measure breathing performance for elderly care.

2. Materials and methods

2.1. Sensor production process

MWCNTs produced by chemical vapor deposition with a diameter of 10–30 nm and a length of 10–20 μm were used in our experiments. The MWCNTs were purified through a process called acid treatment according to Liu et al[15]. The acid treatment could greatly enhance the solubility of MWCNTs by introducing carboxylic (–COOH) functional groups to the sidewalls and ends of MWCNTs[16]. Then, the production of the sensor was divided into two stages. Stage 1 was growth of silicon dioxide (SiO_2) of 100 nm thickness as an insulating base on a silicon wafer with high thermal heat. The SiO_2 was modified by a surface detergent, i.e., 3-aminopropyltriethoxysilane (APTES), which formed a self-assembled monolayer (SAM) on the surface of SiO_2. The amino-terminated groups of the APTES adsorbed on the surface of SiO_2 protruded externally and could facilitate the chemical bonding between MWCNTs and SiO_2. Through this bonding, CNTs were immobilized on SiO_2 to form the thin film for breath sensing. Stage two was implementation of interdigitated electrodes (IDEs) with chromium (Cr, 40 nm) and gold (Au, 300 nm) on the deposited MWCNT networks. This procedure included deposition of Cr and Au layers by sputtering, pattern by photolithography, and etching by lift-off to form IDEs on the MWCNT network to develop microparallel electrodes. The fingers of the IDEs were 120 μm long and 8 μm wide with a gap of 10 μm in between. These IDEs had been electrically contacted to a printed circuit board (PCB) by wire bonding. Thus the final product was done and is schematically shown in Fig. 1.

2.2. Measurement set-up

An integrated experimental platform with the CNT-based nanoelectromechanical system (NEMS) is shown in Fig. 2. It is designed for detecting variable simulated human breath. The experiments

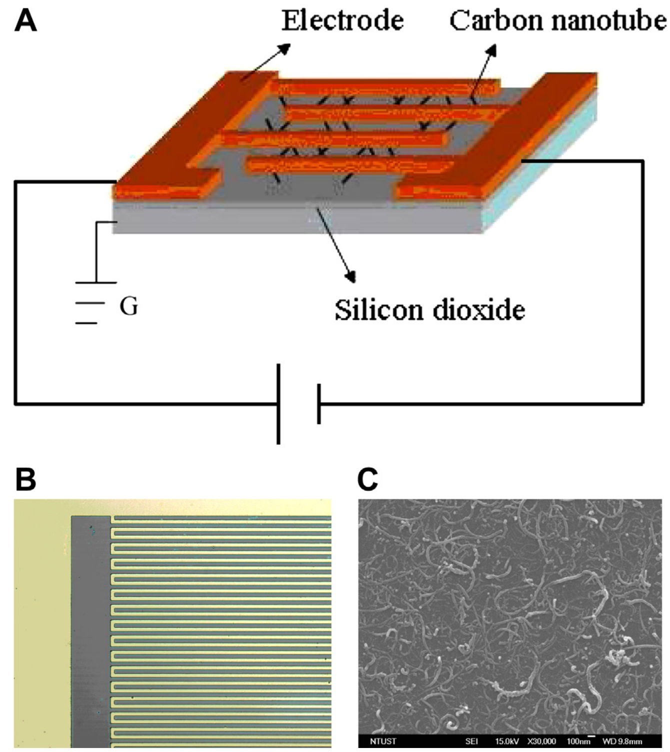

Fig. 1. (A) Multiwalled carbon nanotubes (MWCNT)-based sensor is composed of CNT networks immobilized onto a thin silicon dioxide (SiO_2) film, based on the silicon wafer. Metallic interdigitated electrodes (IDE) were implemented on the CNT networks. (B) The optical microscopic top view image of the IDE on Si/SiO_2. (C) Scanning electronic microscopy image of the MWCNT film. G = ground.

were carried out in the decontaminated box in which the temperature, pressure, and relative humidity could be checked conveniently. The CNT-based sensor, as an airflow transformer mounted on the tip of the central bar in the testing box, was placed 5 cm from the outlet of the air-connecting tube and its miniaturized detection plane of the CNT networks is parallel to the exhaled breath flow. The presentations of breathing activity were transformed to digital change of resistance or voltage through processing of a Keithley 2000 multimeter. The experimental environments were set under room air temperature, atmosphere pressure, and relative humidity. A programmed microchip processor (Microchip Technology Inc., Microchip app025 pic16F series development board) with amplification of the warning signals, when breathing rate was abnormal, were used. According to the US Food and Drug Administration, apnea was defined as cessation of respiratory air flow lasting for 10 seconds or more[17]. Therefore, the cut-off point of the device was set to give warning signals when the breathing rate was less than six breaths per minute. Tests that gave warning upon detection of high-frequency breathing rates were abandoned in this study because of the unclear definition of a high breathing rate and fewer medical contributions in clinical aspects. Benchmarking checks of sensor were done in order to check the stochastic environmental noises on each testing day. During tests, the surface of Si base was grounded to prevent charge accumulation. We measured the responses of the sensor to breaths through monitoring output electronic parameters, resistance (R) or voltage (V) as a function of time (t), i.e., R-t and V-t patterns.

2.3. Patients and experiments

In earlier, preliminary works, we corrected and adjusted the basic working parameters and processing ability of the integrated

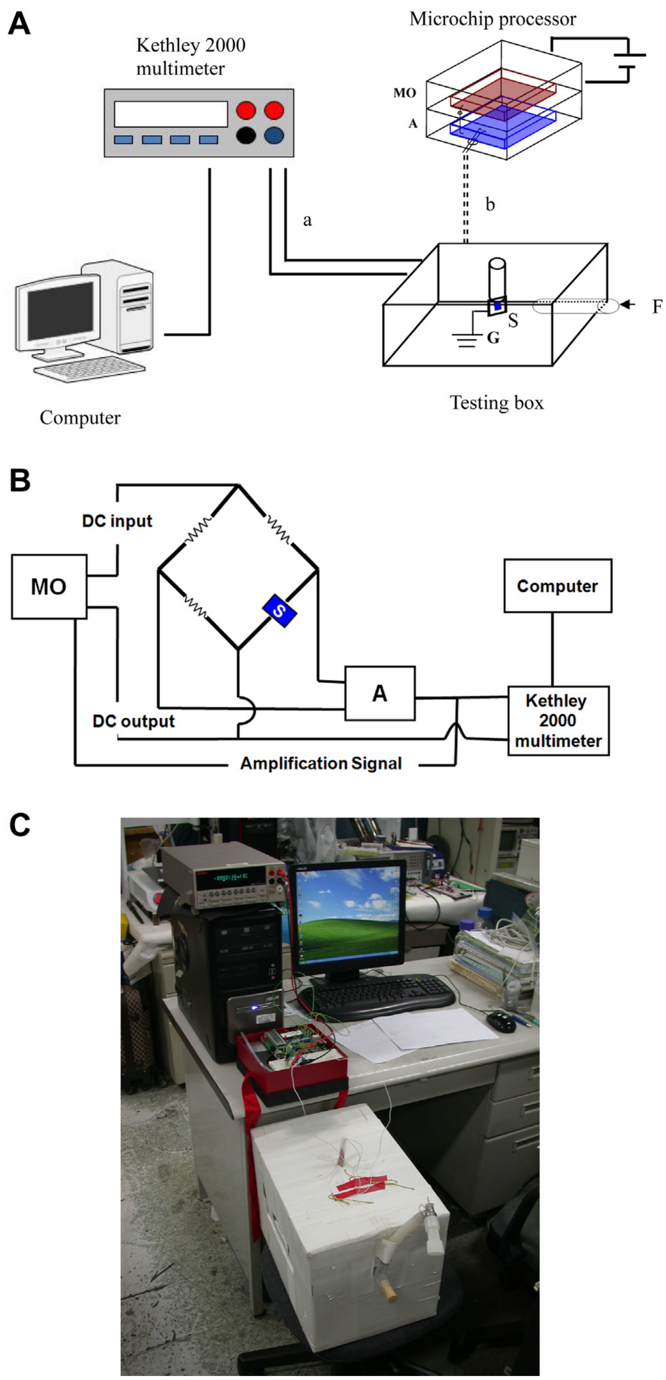

Fig. 2. Schematic diagram for the testing platform. (A) The components of this electromechanical system include a testing box, Keithley 2000 multimeter, computer, and microchip processor. In basic performance of the breath sensor, the testing box is connected to the Keithley 2000 multimeter (solid lines a), while in apnea monitoring, the testing box is extended by parallel connection to the microchip processor (dotted lines b). (B) Diagram of the CMOS circuit for the testing platform. (C) Practical configuration of experimental NEMS. A = amplifier; F = breath flow; G = ground; S = CNT sensor; MO = microchip operator; NEMS = nano-electromechanical system.

system through measurements from young healthy volunteers. To test the reproducibility of performance of this NEMS for breaths from elderly people, elderly volunteers ($\geqq$65 years old) of different sex, age, liver capacity, and other physical conditions were recruited. The inclusion criteria included the ability to tentatively perform self-controlled breathing. Although current measurements only tested the exhaled human breaths, volunteers with respiratory infection and poorly controlled cardiopulmonary function were excluded from the study. A new air-connecting tube was used for each volunteer. We designed several simulated patterns of breathing to check the work and efficacy of the device (Table 1). Pattern 1 was normal breathing. Pattern 2 was 3 minutes of abnormal breathing at less than 6 breaths per minute. Pattern 3 was 3 minutes of normal breathing, then 2 minutes of abnormal breathing followed by 1 minute of normal breathing. Pattern 4 was 2 minutes of abnormal breathing followed by 1 minute of randomly unnatural breathing. Each volunteer was tested at least three times in each specially designed pattern of simulated breathing. Exercising breaths were permitted before recording for psychological and cognitive reasons. The results are expressed as sensitivity rate, i.e., successful numbers divided by testing numbers.

Table 1
Patterns of simulated breath tests.

Breathing pattern	First minute	Second minute	Third minute
1	Normal[a]	Normal	Normal
2	Abnormal	Apnea[b]	Apnea
3	Normal	Apnea	Apnea
4	Randomly abnormal[c]	Apnea	Apnea

[a] Normal breathing rate: 7–12 breaths/min.
[b] Apnea breathing rate: <6 breaths/min.
[c] Randomly abnormal breathing rate >12 breaths/min.

3. Results

3.1. Basic sensor operation

The results of this testing platform showed that the NEMS can be effectively used as a breath monitor. The representative performance of the CNT networks to breath flow is shown in Fig. 3. The changes of electrical properties on the CNT networks reflected that

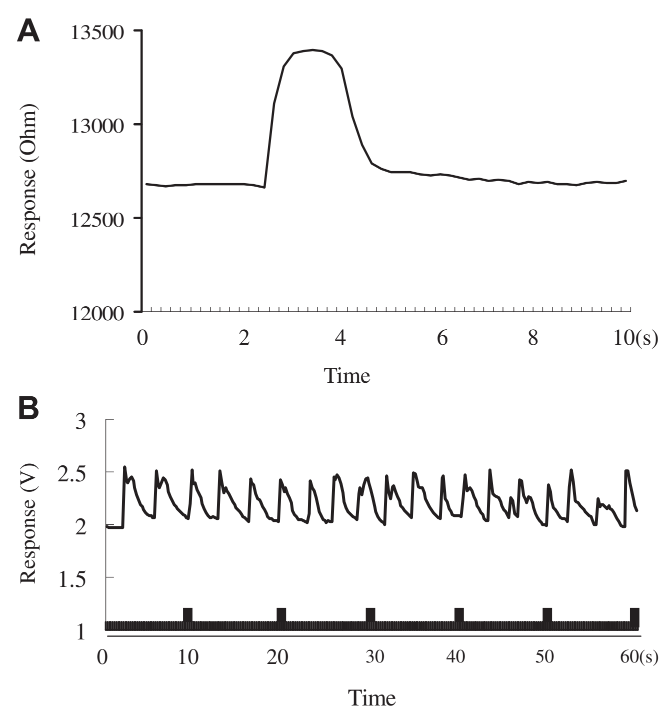

Fig. 3. (A) Basic performance of the multiwalled carbon nanotubes sensor which shows apparent change of electrical resistance to breath, with low ambient noise. (B) Reproducibility test of the sensor.

the response of the sensor to the breath flow, presenting with a high peak wave, was more apparent than that of ambient noise, the flat part of the curve. This result indicates its favorable anti-interference ability with respect to surrounding stochastic noises. In reproducibility tests, the CNT sensor gave similar results of electrical field change both on the same day and on different days. As to each recorded wave, it showed unique characteristic components according to individual performance parameters, such as dynamic changes of strength, flow rate, and exhaled breath compositions. That is to say that no two waves created by different breaths, whether from the same or another volunteer, showed the same curve because of different breathing parameters. The unique breath presentation of the MWCNT sensor indicated that this sensor could be used as a "fingerprint" recorder.

3.2. *Human-device works*

There were 15 volunteers (9 males and 6 females) tested in the simulated warning measurements of this integrated platform. The characteristics of the volunteers are shown in Table 2. After aforementioned adjustments of the programmed microchip operator (by young volunteers), measurements for detection of simulated breath showed high sensitivity and accuracy of this CNT-based NEMS for all volunteers. The successful (sensitivity) rate is 100%. Pattern 1 showed a normal breathing pattern for which the warning system of the device, as expected, did not trigger signals (Fig. 4). When the breathing rate was abnormal (less than 6 breaths per minute), the situation evoked the device's alarm signals (warning sound and red light). When testing a changing breathing rate from unnaturally high frequency to abnormally low frequency (less than 6 times per minute), the device's warning system still worked effectively (Fig. 5). These results show that the integrated NEMS composed of MWCNT sensor and programmed microchip processor could effectively detect the abnormal conditions of apnea.

4. Discussion

The usefulness for this warning platform is based on the unique characteristics of CNT sensors to detect breath. One of the main issues is the specific response of the CNTs to the charged particles in the breath components. The other is the special flow pattern of one-way direction for breaths (either "in" or "out"). The anti-interference effect of the CNT sensor to environmental noises ensured that the sensor gave no response during inspiration while, during exhalation, reacting sensitively to the volatile organic compound of breath[18] by way of changed electrical properties which can be recorded, analyzed electromechanically and interpreted. In clinical application, a modified design of the testing box is needed, such as miniaturization to the scale of the flow-connecting tubes commonly used in respiratory care. The strength of this kind of breath sensor lies in effective working at the open system of the airway.

Physical, biochemical, and molecular biological methods for medical monitoring and diagnostics have developed rapidly in recent decades[18]. The main works have focused on blood and urine analysis for clinical diagnostics and photoelectrical physiology for hemodynamic care. In comparison, diagnostic care using breath analysis is much less developed and not yet widely applied in clinical practice[19]. However, monitoring of breath is as critical and important as other parameters in the care of acutely ill patients. Comparatively, for patients with mechanical ventilation, instruments working in a closed system through a volume-pressure-controlled machine are well established. However, when recovering from a critical status there is a transitional unstable status

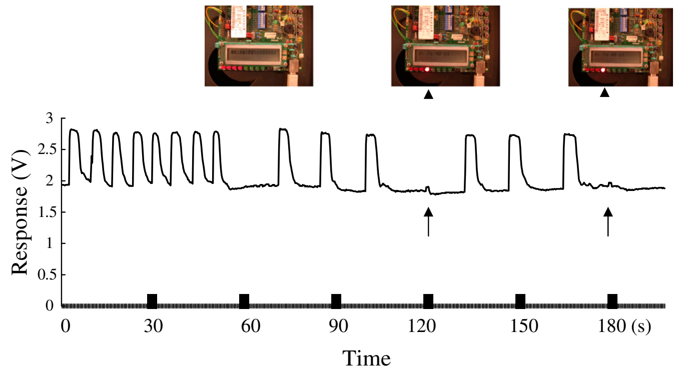

Fig. 4. This diagram shows the nil response of the apnea device to normal breathing (without shining red light), and the response to abnormal breathing [warning sound, shining red light (arrowheads) and warning signals (arrows)].

Table 2
Characteristics of patients.

Patients	Age	Sex	Height (cm) /Weight (kg)	Underlying diseases	Results
1	77	M	172/82	Hypertension Diabetes mellitus COPD	S
2	70	M	173/66	Osteoarthritis	S
3	71	F	156/60	Hypertension Osteoarthritis	S
4	66	M	172/67	Hypertension	S
5	65	F	152/50	Migraine	S
6	66	M	168/64	—	S
7	68	M	172/60	Osteoarthritis	S
8	65	F	158/52	Renal stones	S
9	65	F	155/49	—	S
10	67	M	169/61	Hypertension	S
11[a]	65	M	170/62	Cataract	S
12[a]	67	F	157/50	—	S
13[a]	66	M	166/57	Spondylosis	S
14[a]	65	F	157/53	Hyperlipidemia	S
15[a]	65	M	168/57	GERD	S

COPD = chronic obstructive pulmonary disease; F = female; GERD = gastroesophageal reflux disease; M = male; S = successful measurement.
[a] Tested volunteers without recording by digital transformer (Keithley 2000 multimeter).

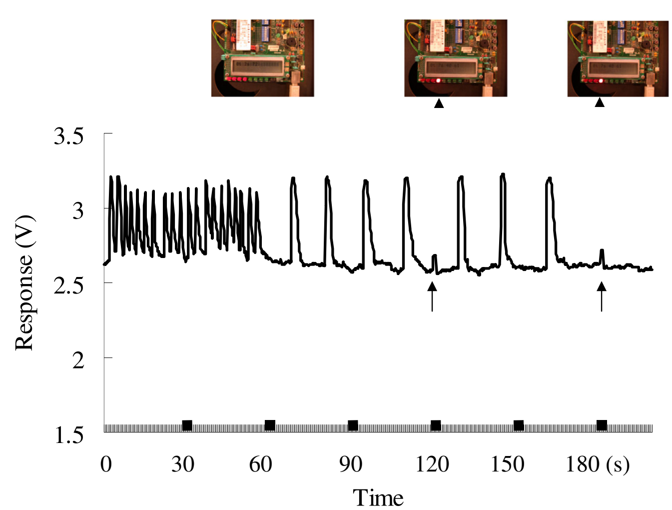

Fig. 5. The warning nano-electromechanical system detects an unnatural breathing rate change from high frequency to abnormal apnea status, which simulates a critical physiological crisis in an elderly volunteer.

which needs to be monitored. In intensive care units (ICUs), monitoring intubated patients is not a problem because there is full support, i.e., oximeter, electrocardiography, sphygmomanometer etc. However, while patients are transferred to regular wards or home care units with fewer facilities, deterioration of the respiratory system (e.g., sputum impaction, tubal obstruction, etc.) is still possible. Therefore a breath monitor, as described in the current research with warning function, high sensitivity, fast response, low cost, high-volume production, high reliability, and suitable for open systems, is still required[11]. The approach described in this paper has not been reported in the literature to the best of our knowledge. Therefore this kind of warning platform can be applied as a base for future smart respiratory care.

The bulk matrix of breath is a mixture of many components which can reflect health conditions and a potential disorder of the individuals[14]. Theoretically, the presentation of the MWCNT sensor to breathing is a summation of a hybrid mechanism incorporating dielectric polarization and gaseous ionization in the miniaturized tip. MWCNTs act as a p-type semiconductor for sensing gas[15,20]. Vaporized molecules adsorbing onto the surface of MWCNTs transfer electrons to MWCNTs and change the electrical properties, resistance or voltage, which can reflect the characteristics of gas/vapor, i.e., entity or flow rate. The electron transfer depletes the concentration of holes in MWCNTs, resulting in an increase of resistance, as shown in Fig. 3. Responses of the CNT sensor have the characteristics of high aspect ratio, small tip ratio, and high conductivity which result from the strong effect of electrical enhancement[21]. Furthermore, the unique presentation of an individual breath by the same individual or another indicates a “fingerprint” record. This kind of specific presentation by a CNT sensor enables effective monitoring of the dynamic changes of performance parameters for breathing (i.e., strength, frequency, and compositions)[13]. Although several reports have disclosed dynamic characteristics of the MWCNT sensor and postulated its applications for breath monitoring[1,11,13,14,18,19]. an integrated device combining an MWCNT sensor and a CMOS operating processor to test human breath has not been reported. Therefore, the results of this experiment highlight that this kind of CNT-based NEMS could be adequately used as an apnea monitor and warning device in elderly people.

In this study, we successfully integrated a programmed microchip processor with an operational amplifier and MWCNT sensor for use in the elderly volunteers, in whom a variety of critical pulmonary dysfunctions may occur. From the results of effective recording and warning, we postulate that improved designs and modification of this kind of electromechanical device could be widely applied in elderly care, both in hospital and at home. Extended and comprehensive clinical practice studies of the combination of new electromechanical nanotechnology and medical science should be warranted for the future of telemedical care.

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