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Telemedical Wearable Sensing Platform for Management of Chronic Venous Disorder

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Abstract—Enabled by emerging wearable sensors, telemedicine can potentially offer personalized medical services to long-term home care or remote clinics in the future, which can be particularly helpful in the management of chronic diseases. The wireless wearable pressure sensing system reported in this article provides an excellent example of such an innovation, whereby periodic or continuous monitoring of interface pressure can be obtained to guide routine compression therapy, the cornerstone of chronic venous disorder management. By applying a novel capacitive, iontronic sensing technology, a flexible, ultrathin, and highly sensitive pressure sensing array is seamlessly incorporated into compression garments for the monitoring of interface pressure. The linear pressure sensing array assesses pressure distribution along the limb in a real-time manner (up to a scanning rate of 5 kHz), and the measurement data can be processed and displayed on a mobile device locally, as well as transmitted through a Bluetooth communication module to a remote clinical service. The proposed interface pressure measuring system provides real-time interface pressure distribution data and can be utilized for both clinical and self-management of compression therapy, where both treatment efficacy and quality assurance can be ascertained.

Keywords—Pressure sensors, Chronic venous disorder, Interface pressure, Micro-electromechanical systems (MEMS), Mobile medicine, Wearable sensing, Capacitive sensors.

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INTRODUCTION

Over the last decade, development of innovative wearable health monitoring solutions has attracted considerable attention in industries and academia, due to growing health awareness, rapid increase of healthcare costs and rising demand for better health services global-wide.[14] Among those solutions, wearable sensors with a capacity of noninvasive and continuous health monitoring that is also comfortable have been the frontier of this trend.[10,26] Applications of such sensors are unlimited, including detecting, monitoring, predicting chronic disease progression, assisting postoperative rehabilitation and evaluating therapeutic outcomes on individual patients.[6,7,29] In this article, we focus on a wearable monitoring solution to address interface pressure monitoring challenge in chronic venous disorder, as one example of such innovative solutions, where the compression therapy for chronic venous disorder is guided by periodic/continuous monitoring of interface pressure.

To evaluate the interfacial pressure in chronic venous disorder currently, there are three companies worldwide providing interface pressure sensing devices: PicoPress® (Microlab, Padua, Italy), Kikuhime® (Meditrade, Soro, Denmark) and SIGaT-Tester® (Ganzoni-Sigvaris, St. Gallen, Switzerland). PicoPress®, Kikuhime® and SIGaT-Tester® all utilize airbags in their systems. The airbag that is inserted between the limb and the bandage is filled with air during the measurement, and a transducer that measures the pressure in the airbag quantifies the interfacial pressure applied to the skin by the bandage.[3,8,27]

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While current interface pressure measurement systems for chronic venous disorder use the pneumatic principle to conduct measurements, these bulky pumping systems generally cannot be worn comfortably for extended periods of time. Moreover, the airbag is filled with air during each measurement, thus making the pressure measurement unreliable over time, as the airbag creates an indentation into the skin. Additionally, the sensors can only provide an average pressure at the location of the sensor, rather than the actual pressure distribution of the entire limb.

Wearable sensors have been increasingly utilized in health monitoring and prosthetic devices. Unlike solid-state sensors, their adaptable and conformable nature can be beneficial when applied to biological surfaces with varying geometries and topologies. Such applications include wearable heart rate monitoring (through electrocardiogram or photoplethysmogram), tracking of muscle movement (using stretchable conductors), and recording of skin temperature (with tattoo-like sensors).[13,21,31,32,35,5,37] For example, polyvinylidene fluoride (PVDF), a polymeric piezoelectric material, has been fabricated into pressure sensors, but the charge leaking of the PVDF film leads to poor DC performance.[30] Rogers' group presented flexible and stretchable electronic sensors for both skin thermal temperature and muscle stimuli monitoring.[17,35] Zhu's and Suo's groups used stretchable conductive material to monitor the bending and the pressure distribution of the body.[32,37] Kim's group designed a multifunctional wearable device to adhere to the skin and analyze movement disorders while delivering appropriate therapeutic drug through a feedback control.[31] As many new wearable sensors have been developed for health monitoring as non-medical devices, there is a pressing demand for further development of clinically-ready wearable devices for the management of chronic diseases over aging populations globally.[3]

Here, we have developed the first wearable pressure sensing platform for interface pressure measurement for venous leg ulceration (VLU). The novel pressure sensor, enabled by an interfacial capacitive sensing principle, is structurally simple, mechanically flexible, optically transparent, and highly sensitive to pressure variation. The sensor essentially relies on the capacitive change between an elastic interface between an ionic gel and a flexible electrode. Figure 1a shows a schematic illustration of the flexible iontronic sensing assay (1 × 8). The thin flexible device packaging allows it to be easily incorporated into a compression bandage, as shown in Fig. 1b. Ionic gel droplets function as the sensing elements and are patterned and encapsulated by two 125-μm thick conductive Indium tin oxide

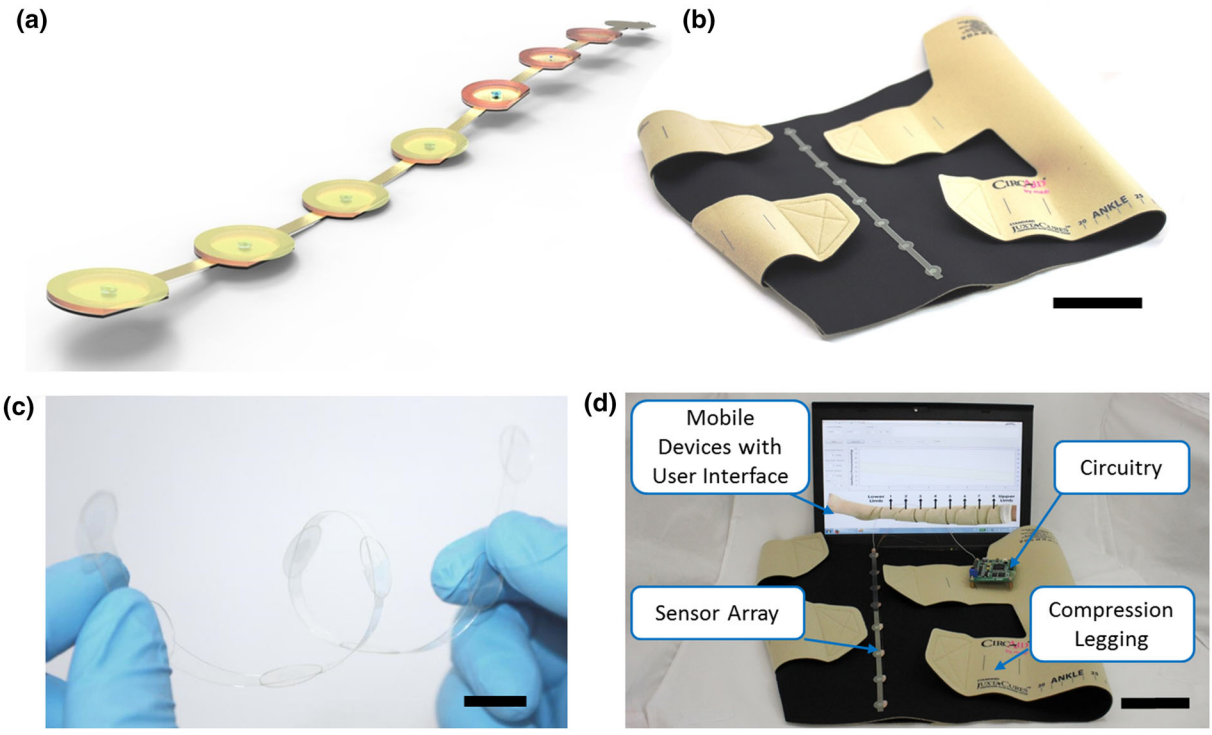

FIGURE 1. (a) Schematic illustration of the iontronic device structure; (b) photo of a Circaid® (Whitsett, NC) commercial inelastic legging integrated with the iontronic flexible sensing array. Scale bar is 10 cm. (c) Photo of the 1 × 8 array sensor. Scale bar is 1 cm. (d) Photo of the whole interface pressure monitoring system. Scale bar is 10 cm.

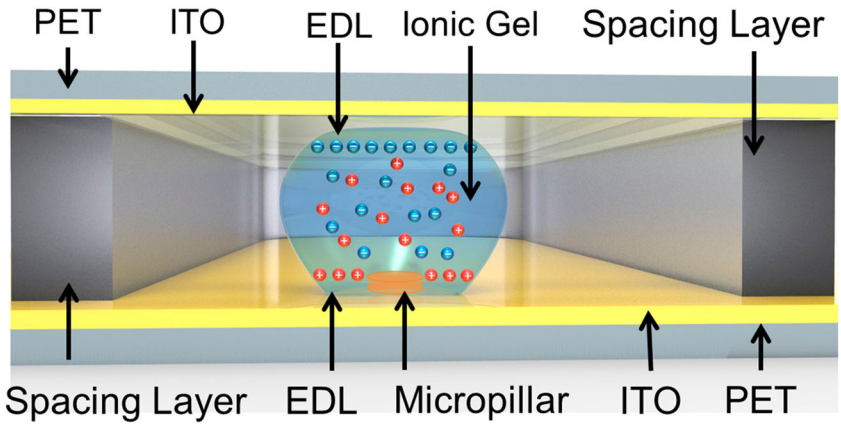

FIGURE 2. A cross-sectional sketch of iontronic sensor structure. The EDL capacitance is simultaneously established at the ionic gel-electrode contact.

(ITO)-coated polymer films as the electrodes. The flexible iontronic sensor has been implemented to address the aforementioned challenges in the existing devices by offering (a) mechanical flexibility in an ultrathin (as thin as 300 μm) package for extended wearable usage (comfort); (b) wireless data processing capacity as a standalone unit, which eliminates the need for additional accessories (e.g., airbags and pumps) (wearableness), and (c) distributed pressure measurement through an array of linear pressure sensing units along the entire limb (multiplicity). Importantly, the iontronic device not only can achieve a high device sensitivity of 0.2 nF/mmHg, but also responds to mechanical stimuli with a response time on the orders of milliseconds. The detection range of the sensor is adjustable, and has been set between 0 and 80 mmHg to match the clinical compression therapy requirements, which typically range from 20 to 60 mmHg.[28] As a demonstration, the iontronic pressure sensing array integrated with a wireless communication module has been applied to interface pressure monitoring, where the pressure under a compression bandage can be wirelessly transmitted and displayed for further clinical analysis and treatment.

MATERIALS AND METHODS

Operation Principle

Figure 2 shows the functional structure of a single unit of the iontronic pressure sensor. The sensor is composed of a nanoliter ionic gel droplet sandwiched between the top and bottom flexible polyethylene terephthalate (PET) membranes (thickness 125 μm). A spacing layer of a 50-μm thick adhesive film supports the separation between the two sensing membranes. On one side of the membrane, a 10-μm high 200-μm wide micropillar acts as the anchor for the iontronic droplet. Electrical double layer (EDL) capacitance is immediately formed upon the contact between the ionic gel droplet and the conductive electrode.[18,32] Under external mechanical loads, the polymer membranes deform, leading to the circumferential expansion of the ionic gel droplet. The variation in the contact area between the ionic gel and electrode surface results in a proportional change in the interfacial EDL capacitance.[23] The relationship between the contact pressure and device capacitance can be modeled theoretically by analyzing the membrane deformation under external pressure and the corresponding capacitance change of the EDL interface.[22] For pressure-induced membrane deformation, the membrane mechanical behavior is well predicted by the classic thin-plate theory.[9] The relationship between the capacitive change (ΔC) and the pressure applied (P) can be derived and expressed as:

$$\Delta C = C_0\left(\frac{H}{H - K \cdot P} - 1\right), \tag{1}$$

where P is the pressure, $K = 3a^4(1 - v^2)/16Eh^3$ is a constant derived from the design parameters, a and h are the radius and the thickness of the sensing membrane respectively, and E and v are the Young's modulus and the Poisson ratio of the membrane material respectively. H represents the original ionic gel droplet thickness before deformation, whereas C_0 is the initial electrical capacitance of the sensing unit before force is applied.

To obtain pressure distribution along the limb, a 1×8 sensing array with 3 cm intervals has been designed to achieve a pressure distribution over a 25 cm length, the average length of adult lower limbs. To establish the optimal pressure measurement range between 0 and 80 mmHg, each droplet sensing unit has

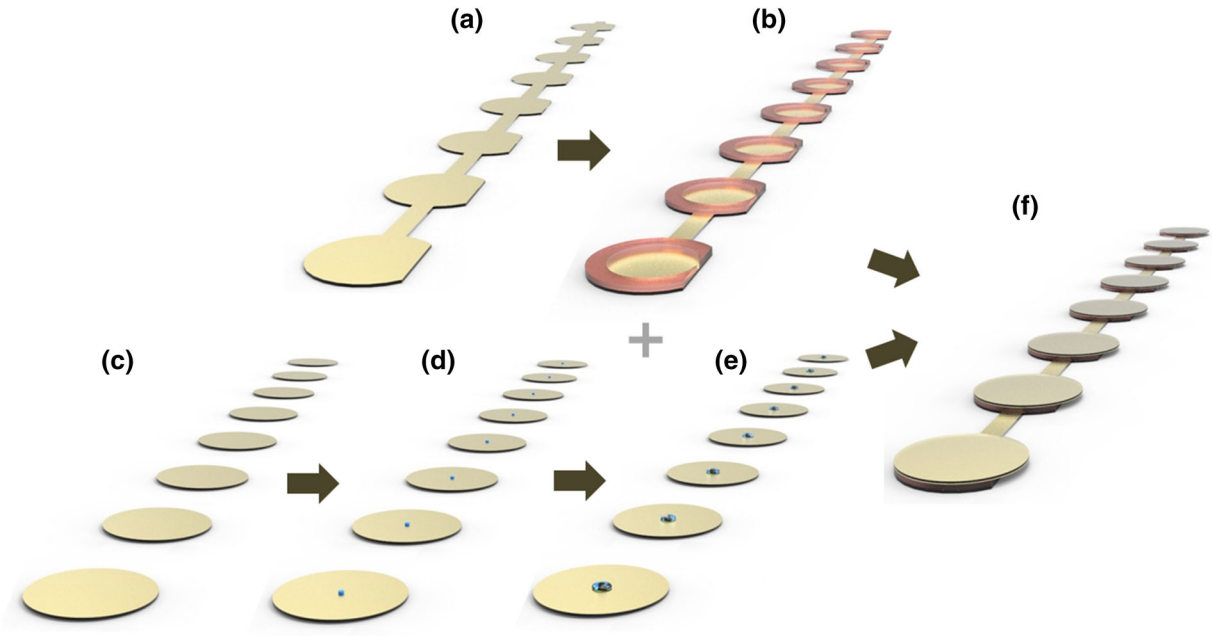

FIGURE 3. Fabrication process of the 1 by 8 iontronic pressure sensor array. (a) Laser-machine ITO on PET substrate as bottom electrode. (b) Laminate transfer adhesive tape on bottom electrode. (c) Laser-machine ITO/PET as top electrode membrane. (d) Photo-lithography polymer micropillar on top electrode membrane. (e) Microfluidic impact printing nanoliter droplets on electrode membrane. (f) Align and assemble two electrode membranes.

a circular sensing chamber of 5 mm in diameter for the interface pressure measurement, based on theoretical analysis.

Fabrication Process

The fabrication process begins with a 125 μm thick transparent PET film with ITO coating (Sigma Aldrich), which is laser-machined (VersaLaser, Universal Laser) into the designated geometries of the bottom membranes of the device as shown in Fig. 3a. In the subsequent step, a layer of 50 μm adhesive transfer tape (3 M 467MP) is trimmed into a 'C' shape and laminated onto the bottom membrane, shown in Fig. 3b. Circular-shaped PET/ITO films are consecutively cut by laser to form the top membrane (Fig. 3c). After the completion of electrode patterning, the polymer micropillar of 10 μm in height is constructed by laminating a negative dry-film photoresist (PerMX3010, DuPont) onto the electrode surfaces on the bottom membrane. Photolithography process is conducted to form the micropillar structure. The micropillar with 250 μm in diameter stays on the bottom membrane as the anchor structure after the developing process using propylene glycol monomethyl ether acetate (>99.5%, Sigma-Aldrich) (Fig. 3d).[25] The ionic gel material is prepared by mixing ionic liquid (1-ethyl-3-methylimidazolium tricyanomethanide, Iolitec), Poly(ethylene glycol) (n) diacrylate (n = 4000, Polysciences, Inc.) and photo-initiator (2-hydroxy-2-methylpropiophenone, Sigma-Aldrich) in a volume ratio of 5:1:1.[2] Using a microfluidic impact printing technique, nanoliter droplets (~7 nL) of the liquid mixture are sequentially deposited onto the micropillar and undergo UV exposure for 20 s (365 nm, 22 mJ/cm^2, ABM, Inc.).[11] After the liquid mixture is fully cross-linked into a single ionic gel droplet, the two electrode membranes are manually aligned and subsequently packaged along the perimeter of each unit.

Wireless Circuitry

A readout circuitry with a wireless communication module (Bluetooth) has been developed to achieve data acquisition and wireless transmission. As shown in the schematic drawing in Fig. 4a, the readout circuitry consists of an analog front, microcontroller and Bluetooth 2.0 transmission module. The analog front is devised to interrogate each capacitive sensing element of the iontronic sensing array consecutively, from which the collective interface pressure data are sampled into the digital circuitry. Given an array of 1 × 8 iontronic sensors, the analog front can provide a sampling rate of 40,000 Hz (with 625 readings/unit/s). Figure 4b illustrates the schematic of the acquisition circuitry with the equivalent circuit model of a three units sensing array embedded. Due to EDL capacitance at the electrode–electrolyte interface and ionic resistance inside the droplet, each sensing unit can be

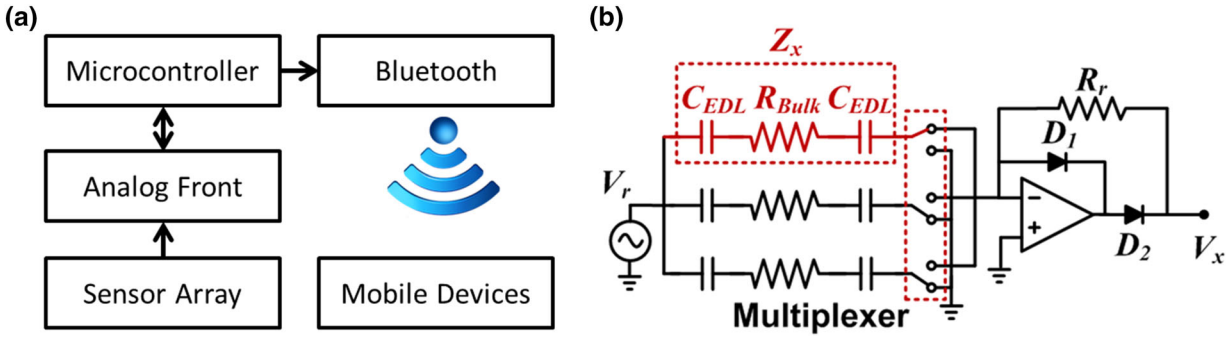

FIGURE 4. (a) Schematic drawing of the wireless circuitry. (b) Schematic drawing of the analog-front circuitry. Each sensing unit consists of two EDL capacitors (C_{EDL}) and liquid bulk resistor (R_{Bulk}) in series, together regarded as an impedance of Z_x. The active sensing unit by the multiplexer has been shown in red. Input signal (V_r) passes through the active sensing unit, is rectified by a rectifier, amplified by an op-amp, and finally feeds to the output as V_x.

modeled equivalently to two EDL capacitors (C_{EDL}) and liquid bulk resistor (R_{Bulk}) in series, which can be combined together and regarded as an overall impedance of Z_x.[23] As illustrated, all sensing units are powered under a common AC input (V_r). To address an individual sensing unit, the corresponding multiplexer can be steered and switched on by the micro controller unit (MCU), from which a corresponding output voltage (V_x) is generated, amplified and conditioned. The output voltage is supposed to follow a linear relationship with the corresponding impedance change (Z_x) in the measuring unit, which can be expressed as:

$$V_x = -V_r \frac{Z_x}{R_r} \tag{2}$$

where R_r represents a reference resistor in the amplification circuitry. In addition, two diodes (D_1 and D_2) establish a half-wave precision rectification circuit.[1] The rectified voltage output from the inverting amplifier is acquired by the microcontroller digitally (MSP430, TI). As the MCU-controlled multiplexer repeatedly scans through each sensor, the impedance value of each corresponding unit is acquired accordingly. Eventually, the Bluetooth module connected to the microcontroller transmits digital pressure data *via* a multi-channel protocol to a custom user interface on mobile devices. The signal-to-noise ratio (SNR) has been characterized by measuring 400 continuous data points from a single unit sensor using this circuit. The resulted SNR is better than 48 dB, as shown in Fig. S1. Further improvement on the SNR can be achieved by adding higher order filters in data processing.[34]

Graphic User Interface

Graphic user interface (GUI) of the wearable pressure sensing platform conducts multi-thread receiving, parsing, processing, and rendering real-time data to users.[16] It is programmed in Microsoft C#. During the initial setup of the GUI, the clinician and/or the patient predefines the optimal interface pressure range and programs it accordingly. The GUI program using this predefined pressure range automatically calculates the targeted pressure distribution, thus truly customizing compression therapy along the limb being treated. As the patient gradually wraps the bandage onto the limb through the lower section as suggested by the manufacturer, the embedded pressure sensors will provide simultaneous readouts of the interface pressure and wirelessly transmit and display the data onto a mobile device. Figure 5 illustrates the current GUI design for the wearable sensors in which the pressure columns (in Y axis) indicate the corresponding readings from the wearable sensing units (along X axis). The calculated compression pressure range for each wrapping section is confined between the two dotted lines. When the applied pressure is either lower or higher than the targeted pressure range, the indication bar turns red. Once the interface pressure falls in the preset range, the corresponding pressure bar becomes green. In summary, this GUI will allow management and monitoring of the pressure distribution along the patient's limb during the compression therapy in a visible and straightforward fashion.

Device Characterization

Device sensitivity was characterized by investigating the relationship between pressures applied onto the device surface and the change in capacitance of the ionic gel sensing unit. The experimental characterization and calibration were conducted on the single unit device. Five samples were prepared for the characterization. Each measurement of the device sensitivity was repeated three times. The device under test was placed onto a mannequin limb adjacent to a standard manometry bladder (Kikuhime™, MediCad) and

wrapped under a manual pressure cuff. By externally pumping air into the pressure cuff, interface pressure on the mannequin surface can be artificially elevated, from which the pressure readings were referenced to the readouts of Kikuhime™ device, while the capacitive values of the iontronic sensor were directly assessed by a LCR meter (4284A, Agilent).

Characterization of the device response time was conducted by using a piezoelectric actuator (T215-A4-303, Piezo Systems) which provided a periodic movement (up to 50 Hz) with a travel distance up to 200 μm. The piezoelectric actuator was driven by an 80 V peak-to-peak square wave from 1 to 50 Hz for the device calibration.

Cyclic testing was conducted to verify the device repeatability using the same experimental setup as described in the response time measurement. The devices were challenged for more than 10,000 cycles under 20 Hz periodical stimuli.

All experiments involving human subjects were conducted under approval from Institutional Review Board at the University of California, Davis (protocol number: #776240-1). One testing volunteer was tested under a relaxed sitting position, wrapped with the iontronic sensing array integrated inelastic legging. The embedded Velcro® fastener has been used to adjust the tightness of the band and the level of the compression applied along the limb.

RESULTS

Device Sensitivity

Device sensitivity of the iontronic pressure sensor was defined as the capacitive change (ΔC) vs. pressure load (P) on the device. With a circular sensing membrane of 5 mm in diameter and 125 μm in thickness and a separation layer of 50 μm in height, the iontronic sensor exhibited a device sensitivity of approximately 0.2 nF/mmHg. Figure 6 summarized the measurement results (dots) of the pressure-capacitance ($P - \Delta C$) relation compared with the theoretical predictions (solid line). As shown, the capacitive change of the iontronic device progressively increased to around 12 nF as the external pressure elevated from 0 to 60 mmHg. During this range, the pressure-capacitance measurements closely followed with the theoretical predications presented in Eq. (1). Further increase in the pressure load caused a noticeable deviation from the capacitive measurement. This divergence may likely attribute to the fact that the sensing membrane deformation went beyond the small deflection limits governed in the thin plate theory.[33] The pressure correlation has been analyzed from the pressure readouts from a commercial Picopress device (Microlab, Padua, Italy) and our system, as shown in Fig. S2. A statistical (Student's T test) analysis from these results shows that the p value is greater than 0.05, indicating no significant difference between two systems.

Mechanical Response Time

Characterization of the device response time along with cyclic test of the iontronic pressure sensor was conducted experimentally, which illustrated the dynamic response and repeatability of the sensor, respectively. For the response time measurements, as shown in Figs. 7a–7c, the capacitive change of the device rapidly responded to periodic mechanical stimuli with frequencies from 1 to 50 Hz, which indicated that the device can realize a mechanical response time in a few millisecond range. Such a frequency response performance suggested that the device not only can

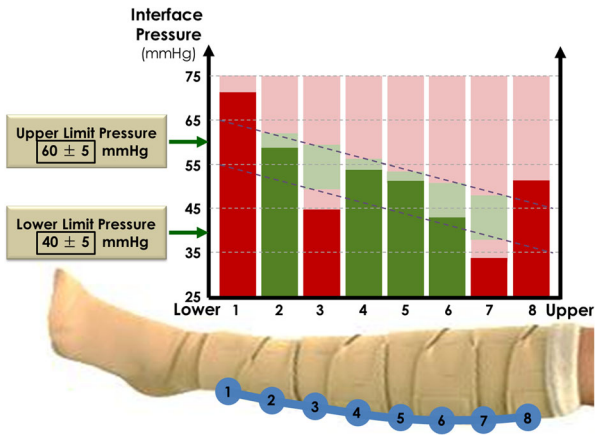

FIGURE 5. Illustration of the graphic user interface prototype of the interface pressure monitoring.

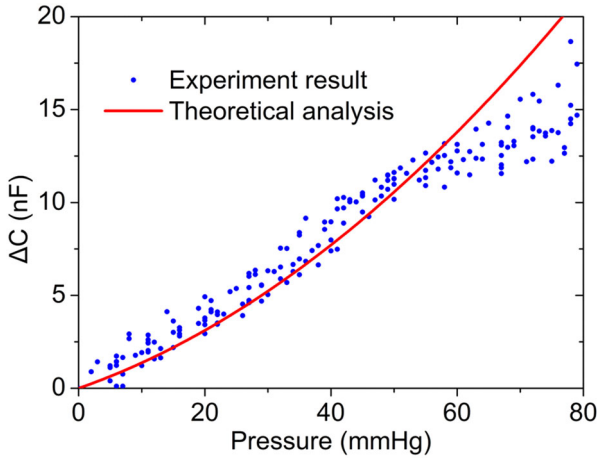

FIGURE 6. Measurement results (dots) and theoretical predictions (lines) of the pressure-capacitance ($P - \Delta C$) relation for characterization of the device sensitivity.

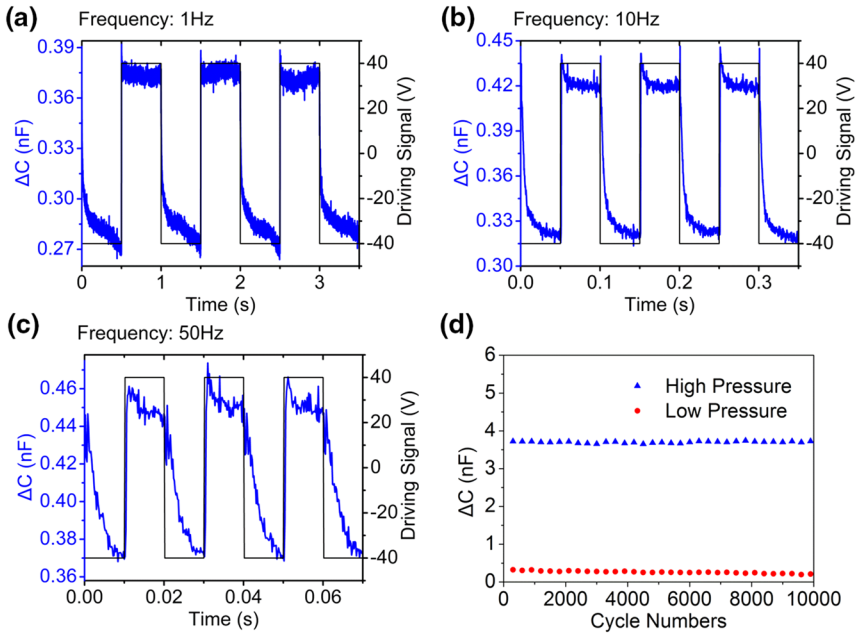

FIGURE 7. Measurements of mechanical response times of the iontronic device under periodic stimuli of (a) 1 Hz, (b) 10 Hz, and (c) 50 Hz, respectively. (d) Repeatability test using the capacitive change as a function of the external pressure cycles under both high and low pressure loads, the mechanical repeatability and reliability of the flexible iontronic sensors.

record static interface pressure, but also capture dynamic pressure variations during patient's movement.[4] Figure 7d showed the repeatability testing result by recording device capacitive change under a cyclic mechanical load for 10,000 cycles. As illustrated, two different levels of pressure loads (high/23 mmHg and low/2 mmHg) were applied onto the device and the capacitive changes of the device were assessed with less than 2% variation as compared to its initial value during the 10,000 testing cycles. 1 mmHg minimally detectable pressure is also been characterized and shown in Fig. S3. This confirmed the excellent mechanical repeatability and reliability of the flexible iontronic sensors.

Pressure Distribution Mapping

A 1 × 8 array of the iontronic sensors is incorporated into a commercially available inelastic legging, Circaid® (Whitsett, NC), for interface pressure mapping during compression therapy. The inelastic legging has been applied to the lower leg with the sensor attached onto the skin-contact side. Figure 8 illustrates the interface pressure measurement setup along with digital pressure mapping for the wearable pressure sensing platform. As illustrated in Fig. 8a, the volunteer is wrapped with the inelastic legging and is tested under a relaxed sitting position. As a testing point, on the Graphic user interface (GUI), the targeted compression pressure for the lower limb section has been set at 40 mmHg and gradually reduced to 20 mmHg towards the upper limb section. In addition, a pressure tolerance of ±10 mmHg has been set to produce an acceptable pressure range along the limb. As the inelastic legging is wrapped around the volunteer's limb, the measured pressure distribution along the limb is simultaneously displayed on the GUI through the wireless linkage. Initially, the volunteer wears the inelastic legging, sits on a chair, and puts one leg in a relaxed state. The embedded Velcro® fastener has been used to adjust the tightness of the band and the level of the compression applied along the limb. As the compression pressure reaches the appropriate preset range, the pressure bars turn green; otherwise they stay as a warning color (red), as shown in Figs. 8b and 8c.

DISCUSSION

Varicose veins and venous hypertension are the leading causes of lower extremity VLU which is the most severe form of chronic venous disorder. It occurs in up to 5% of the population over 65 years of age and 1.5% of the general population.[12,19] Compression therapy remains the main treatment and prevention of VLU, and has a GRADE 1A recommendation from the clinical practice guidelines published by the Society for Vascular Surgery (SVS) and the American Venous Forum (AVF).[15,20,24] Significant challenges remain in

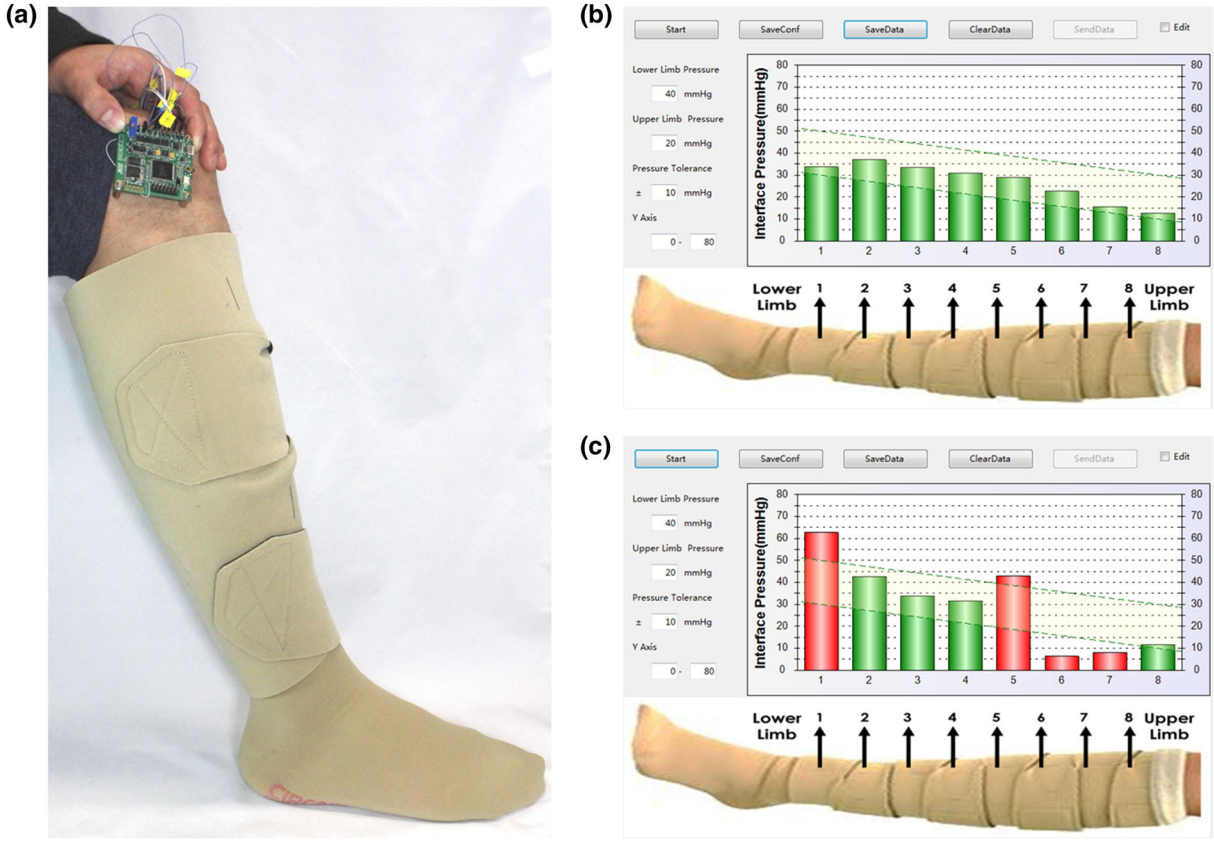

FIGURE 8. (a) Photo of the iontronic sensor integrated inelastic legging on volunteer's limb with readout circuitry. Interface pressure distributions shown on GUI, (b) when the test object manually adjusted the tightness of the elastic bandage to the target pressure range, and (c) when randomly placing on without referring to the target pressure value, respectively.

compression therapy especially regarding the ambiguity in the level of compression pressure applied during bandage changes at each clinical visit. This is often performed by the clinical staff, and due to the lack of consistent pressure measuring devices available, the interfacial pressure may vary between bandage applications. This wearable sensing system overcomes the limitation of conventional interface pressure measurement device for VLU and is inherently invaluable to chronic venous disorder management. First, the iontronic pressure sensor array has an ultrathin and flexible package which can be easily integrated on compression garments and worn comfortably for extended periods of time without requiring a professional operator to adjust interface pressure. Second, the mobile communication capability would allow accurate pressure adjustment with immediate feedback independently in each wrapping section of the limb for more localized compression therapy, which is unavailable in the existing technologies.[27] Furthermore, the multi-unit sensing array provides not only a single point reading as the current interfacial sensing devices do, but also offers pressure distribution data which could be helpful for graduated compression therapy.[36]

CONCLUSIONS

In summary, a wearable body pressure sensing system utilizing a newly invented iontronic pressure sensor array has been developed for interfacial pressure measurement in VLU patients. By integrating the highly sensitive, flexible, ultrathin-profiled sensing array into a classic compression garment, the interface pressure distribution along the lower limb can be easily accessed through a telemetric link in a real-time manner on any mobile device. The sensitivity of the device is characterized at 0.2 nF/mmHg with a millisecond response time, which enables patients or caregivers to monitor the pressure variations during application and adjustment of the compression garments accordingly with visual digital feedbacks. Furthermore, the soft construct with the ultrathin packaging (of 300 μm in thickness) provides an extra level of comfort for continuous wearable sensing, particularly when worn for

extended periods of time during compression therapy. Therefore, such a wearable healthcare solution could be highly attractive to both clinical use and point-of-care management for VLU patients and could have the potential to reduce time and cost of the patients who suffer from the chronic disease for repetitive clinic visits while significantly improving outcomes and evaluations.

ELECTRONIC SUPPLEMENTARY MATERIAL

The online version of this article (doi:10.1007/s10439-015-1498-x) contains supplementary material, which is available to authorized users.

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