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Review

# Patient-specific flexible and stretchable devices for cardiac diagnostics and therapy

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ABSTRACT

Advances in material science techniques and pioneering circuit designs have led to the development of electronic membranes that can form intimate contacts with biological tissues. In this review, we present the range of geometries, sensors, and actuators available for custom configurations of electronic membranes in cardiac applications. Additionally, we highlight the desirable mechanics achieved by such devices that allow the circuits and substrates to deform with the beating heart. These devices unlock opportunities to collect continuous data on the electrical, metabolic, and mechanical state of the heart as well as a platform on which to develop high definition therapeutics.



**Contents**



## 1. Introduction

High-density cardiac mapping has been an important experimental and clinical tool for the identification and the evolution of the understanding of normal conduction and arrhythmia mechanisms. The first electrode heart "socks" were developed in the 1980s for global epicardial electrical mapping. As basic research tools, many of the first sock devices were handmade designs with recording electrodes mounted on synthetic fabric, sewn to loosely fit a ventricle (Harrison et al., 1980; Paul et al., 1990; Wit et al., 1982; Worley et al., 1987). These devices provided an effective tool to increase the spatial resolution of recording propagation patterns. Studies using similar devices have been used to investigate local potential heterogeneities in ischemia transition regions (Swenson et al., 2009), to visualize atrial activation patterns including preferential pathways with temporary silicon sheets of unipolar electrodes (Derakhchan et al., 2001), and a nylon sock has even been used to test cardiac resynchronization therapy (CRT) pacing sites for mechanical resynchronization (Helm et al., 2007). However, due to the dynamic contours of the beating heart, it is difficult to achieve quality contact across the whole epicardial surface with these devices. Although still used frequently in the research setting, these

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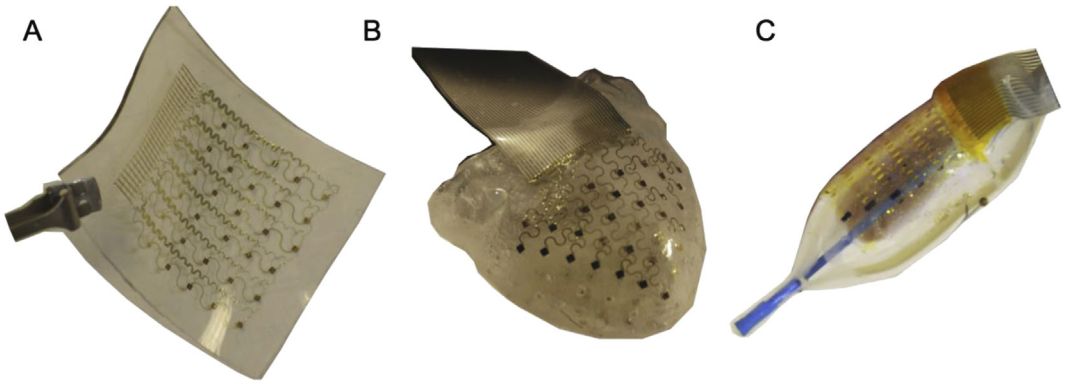


**Fig. 1. Custom Design Option**. Sample geometries for stretchable membrane devices. **A** planar sheet with gold recording electrodes. **B** Epicardial membrane custom design for rabbit heart geometry with gold recording electrodes. **C** Endocardial balloon with gold recording electrodes and $IRO_2$ pH electrodes.

devices have not transitioned to clinical applications and the assembly of the socks still presents limitations including the density of electrode arrays, spatial coverage, and scalable manufacturing. Additionally, it is becoming increasingly evident that the electrical, mechanical and energetic states of the heart should not be studied only in isolation. The interplay of pathophysiological remodeling across many disciplines of cardiac research compels the development of research and clinical tools that can extend beyond high-resolution electrical signals.

Taking advantage of recent advances in materials science fabrication technology and innovative circuit design, a novel platform has emerged for the development of such devices that can monitor multiple parameters simultaneously with high spatial resolution and follow the curvilinear surface of the beating heart (Xu et al., 2014). These devices are built on stretchable contour-fitting membranes custom designed to the geometry of the heart. A diverse array of multiparametric sensors can be placed in custom orientations across the membrane, spanning the entire epicardial surface. The design process can also be tailored to different shapes depending on the intended implementation. Planar sheets, epicardial socks, and balloons have all been tested in the research setting (Fig. 1).

Feasibility tests for these sensors have been executed in ex vivo environments for a variety of cardiac applications and have demonstrated the success of such a platform at simultaneously interrogating many cardiac states for research, diagnostic, or therapeutic use (Chung et al., 2014; Kim et al., 2011a; Xu et al., 2014). Therapeutic electrical stimulation paradigms have long been restricted to 1 or 2 electrode sites. CRT was a sizable step forward with the introduction of simultaneous pacing at two separate sites (Lattuca et al., 1990). However, not all patients respond equally to CRT in its current form (Auricchio and Prinzen, 2011). The devices reviewed here offer a platform for access to an enormous increase in pacing sites and a shift from low definition to high definition electrical therapies. With future development, these membranes can be implemented as near-continuous monitors of cardiac performance, providing clinicians with a set of internal eyes guarding patients' progression into or from disease states by tracking improvement following therapeutic intervention.

### 1.1. Device fabrication

Device fabrication has been discussed in detail previously (Kim et al., 2012, 2011b; Rogers et al., 2010) and here we give an overview of the process. The current cardiac specific membranes build upon previous work at the University of Illinois-Urbana Champaign (UIUC) on soft-contact sensors for epidermal applications (Khang et al., 2006; Kim et al., 2011b). The Rogers' group mastered the art of bonding ultrathin sensors to a substrate with mechanics that match the two-dimensional biological tissue with which it interfaces. The elastomer substrate and the circuits are designed to stretch, twist, and bend to great extremes while maintaining the integrity of the circuit (Fig. 2). Experimental tests illustrating consistent I–V characteristics in a variety of deformed states have been conducted. Furthermore, Finite Element Modeling has been used to study the distributions of strain to guide the design and fabrication of these circuits. Representative examples of such

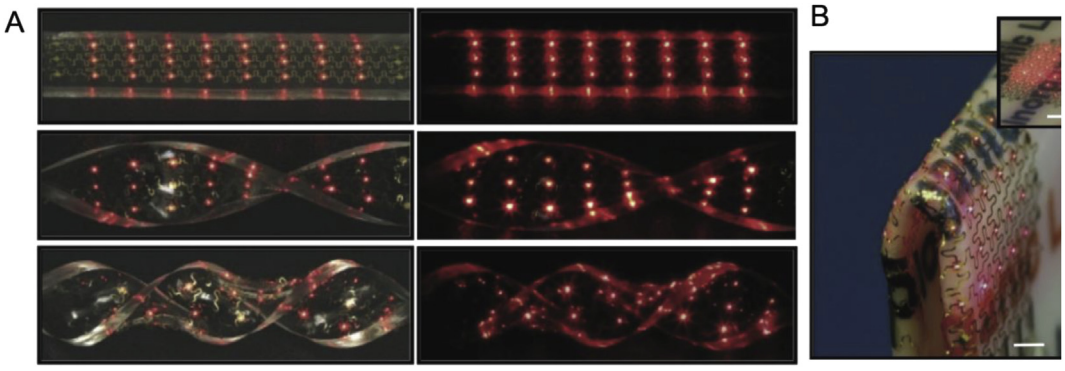


**Fig. 2. Conformability of circuits**. **A** LED circuit in the flat configuration and various degrees of twisting the substrate. Illumination demonstrates integrity of circuit is maintained. **B** LED circuit is bent around a corner. Illumination demonstrates integrity of circuit is maintained. This figure is modified from Kim et al., 2010.

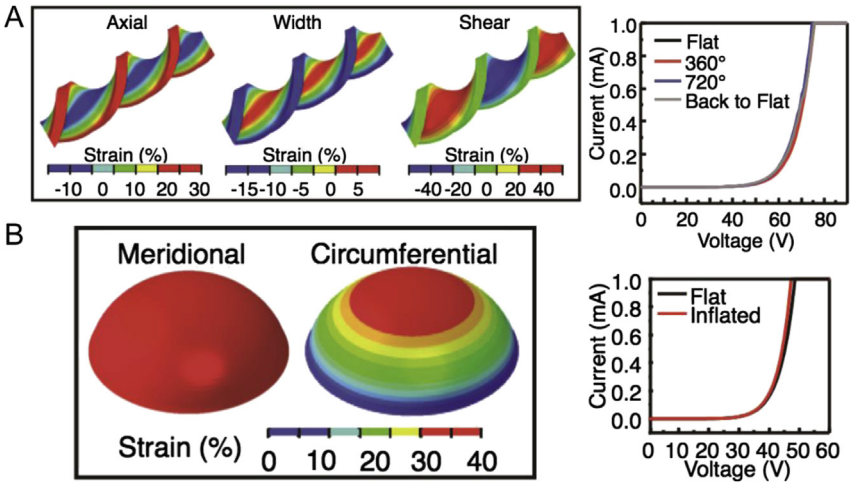


**Fig. 3. Representative Device Mechanics**. **A** Distributions of stain calculated by FEM for 720 degrees of twist and the I–V relationship during twisted and untwisted states. **B** Distribution of strain calculated by FEM for a configuration stretched by inflation and corresponding I–V relationship. Figure modified from Kim et al., 2010.

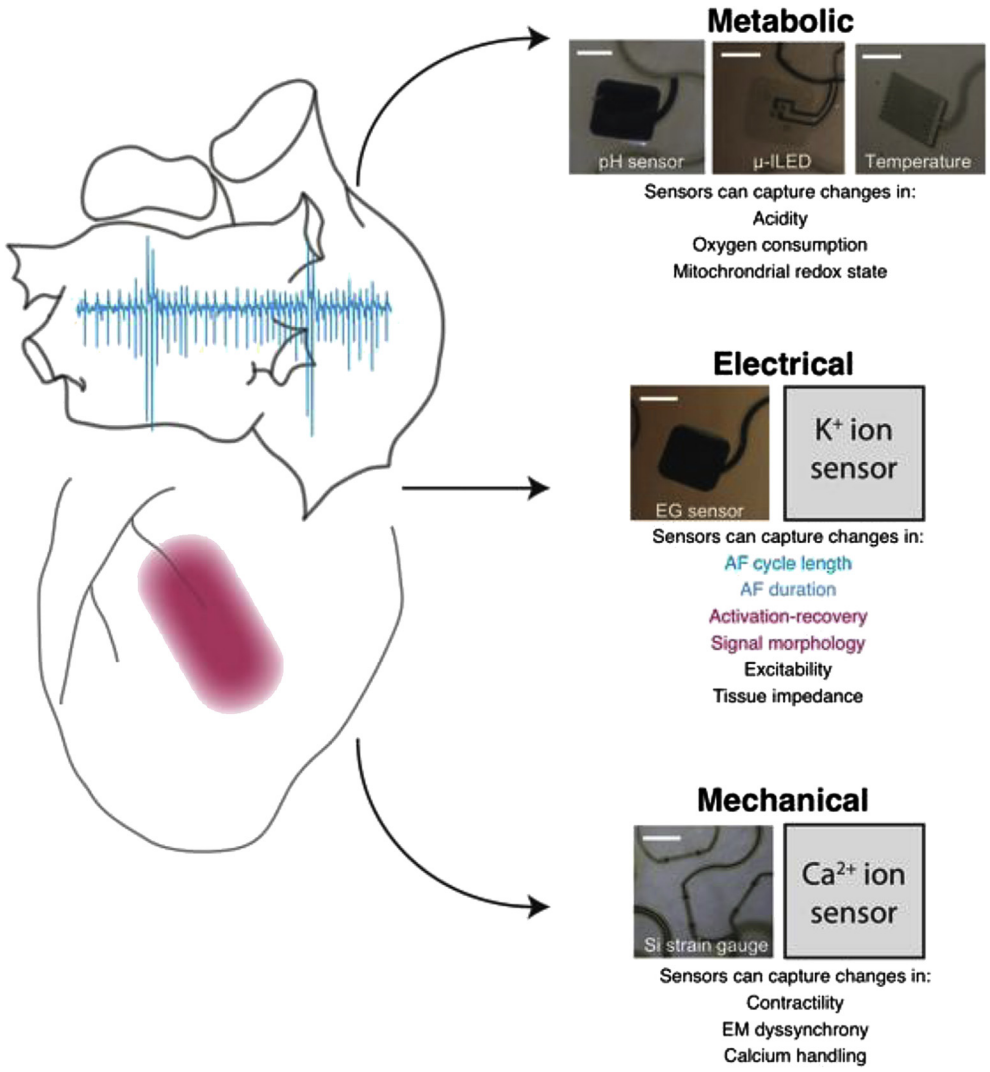


**Fig. 4. Disease States: Atrial Fibrillation and Ischemic Injury**. Schematic shows metabolic, electrical, and mechanical parameters in disease states that can be probed by a variety of specific sensors in a simultaneous fashion. Scale bars, 500 μM. Parts of this figure are modified from Xu et al., 2014.

studies are shown in Fig. 3. Current cardiac devices have evolved to three-dimensional substrates molded to any cardiac-specific shape, including ventricular tissue as well as coronary vessels. Magnetic resonance imaging or computed tomography scans provide the structural geometry for the three-dimensionally printed mold for which the sensors are constructed.

All the sensors are vacuum deposited in planar patterns, then transfer-printed to the elastomer substrate of the desired geometry. The devices reviewed here maintain intimate contact with the heart without significantly constraining function. A serpentine connection design removes the rigidity of the metal wiring, allowing the circuit to stretch with the heart and the substrate on each contraction. The devices have secure holes in the substrate to prevent trapping of fluid between the device and the heart. Additionally, the transparent nature of the device elastomer has optimal optical properties for simultaneous optical imaging or spectroscopy, a key advantage for use in research.

### 1.2. Interplay of cardiac states in disease

The heart is a complex functional syncytium with a series of elements working in unison to reliably perform and respond to conditions of stress. Although much has been gained from isolated cellular studies, the combined functional behavior on the organ level and the interaction between each subsystem is necessary to complete our understanding of disease states of the heart. Both atrial fibrillation (AF) and ischemic injury are excellent examples of the complex network and feedback loops across systems inherent in cardiac disease states and illustrate the need for simultaneous sensing (Fig. 4). AF is strongly associated with self-propagating electrical and structural remodeling (Allessie et al., 2002; Allessie, 1998). Electrically, this is marked by changes in the conduction velocity, the action potential duration and the refractory period; however, there are many additional parameters that may contribute mechanistically to these changes. AF is often associated with atrial dilation on the cellular and the macro scale; changes in wall stress, intra-atrial pressure and activation of stretch receptors may all activate downstream cascades (Wijffels et al., 1997). Additionally AF is marked by severe metabolic changes. Studies have shown increases in oxygen consumption, decreases in atrial reserve flow, mitochondrial deletion and glycogen accumulation (Thijssen et al., 2000). Together these changes significantly impact the energetic state of the atria and alter calcium handling, leading to both electrical and mechanical consequences (Dobrev and Nattel, 2008; Kalifa et al., 2008).

Likewise ischemic injury involves complex changes across many cardiac subsystems. During acute ischemia, the lack of oxygen causes oxidative phosphorylation to stop and forces cardiomyocytes to use glycolysis for ATP production. A byproduct of glycolysis is $H^+$, which is removed from the cell via the $Na^+$-$H^+$ exchanger and consequently leads to a decrease in extracellular pH (Murphy et al., 1991). As ischemia progresses and ATP is consumed in the cytosol, there is an increased probability that sarcolemmal $K_{ATP}$ channels open and increase outward $K^+$ conductance (Nichols et al., 1991). Ultimately, the increase in extracellular $K^+$ leads to shortening of action potential duration, reduction of inward $Ca^{2+}$, and depolarization of the resting membrane potential. In the case of regional ischemia, heterogeneity in resting membrane potential can result in current flow from the ischemic zone to normal myocardium, which can initiate ectopic activity and lead to reentrant arrhythmias (Janse and Wit, 1989). If ischemia progresses long enough, an infarct will form (Janse and Wit, 1989). The infarct will be mechanically isolated from healthy myocardium and will move passively. Fig. 4 displays the current sensors and also those being developed ($Ca^{2+}$ and $K^+$ sensor) that can be used to investigate the interactions between each subsystem, including metabolic, electrical, and mechanical.

In both disease states electrophysiological, metabolic, and mechanical changes have distinct time courses and spatial dependences, which may help separate cause from consequence and identify those changes that are reversible. A multiparametric array can locally probe these changes simultaneously. These devices could be used to identify critical anatomical regions that indicate the origin of pathophysiological conditions such as arrhythmias, ischemia, or heart failure. These regions can then be used to guide therapeutic interventions.

## 2. Diagnostic applications

For applications related to clinical diagnostics, research interrogations and monitoring engineered tissue constructs a variety of sensors were tested in an ex vivo environment including: electrogram electrodes, pH sensors, and LEDs.

### 2.1. Electrical mapping

High-resolution electrogram mapping is required for tracking activation and repolarization patterns in both the clinical and research setting. Currently there are many approaches to estimating the propagation patterns to aid diagnosis. In 1999 Rudy introduced an algorithm for estimating the epicardial activation from body surface electrograms using inverse problem based calculations (Rudy, 1999). Since then, several groups have continued this line of work and expanded the application to include mapping of repolarization and some therapeutic interventions (Cochet et al., 2014; Sapp et al., 2012; Zhang et al., 2013a). This technique is computationally expensive and requires CT images for the precise location of the body surface electrodes. While clinically beneficial, it does not provide a real-time mapping solution. An alternative approach is using endovascular mapping catheters for endocardial mapping that are on the market or in the development pipeline. With the endovascular approach, it is difficult to achieve a high density or maintain constant, quality contact between the electrodes and the tissue due to the fit and the mechanics of the baskets or sequential probes. Both limitations challenge the reliability of recordings from such devices. Additionally, neither of these techniques provides an opportunity to monitor the patient in a continuous 24/7 fashion, including when they leave the doctor's office. The stretchable membrane platform does offer this possibility. The devices achieve high-resolution electrogram mapping by using 0.25–1.0 $mm^2$ gold electrodes.

The propagation pattern was validated using simultaneous optical mapping; therefore the acquisition of electrograms was used to determine adequate electrode size and spacing for signal quality and effective reproduction of spatial patterns for the membrane devices. In the current design iteration, these devices achieve a spatial resolution of 5 mm with an average signal to noise ratio of >40 dB across both pharmaceutically arrested and beating rabbit hearts. Representative activation maps from these results are shown in Fig. 5. Clinically these devices can be used to map critical regions of arrhythmias based on rotor detection, dominant frequency, regularity, or signal morphology for arrhythmia detection. The electrograms could also pick up regions of progressing ischemia by analyzing signal morphology, in addition to pH and $K^+$ sensors. Additionally, these devices are an ideal research platform for important correlations between clinical extracellular measures and optical estimates of intracellular behavior that are not available to clinicians. The most apparent example is a systematic comparison of action potential duration and various definitions of activation recovery interval, considering the effect of T-wave morphology

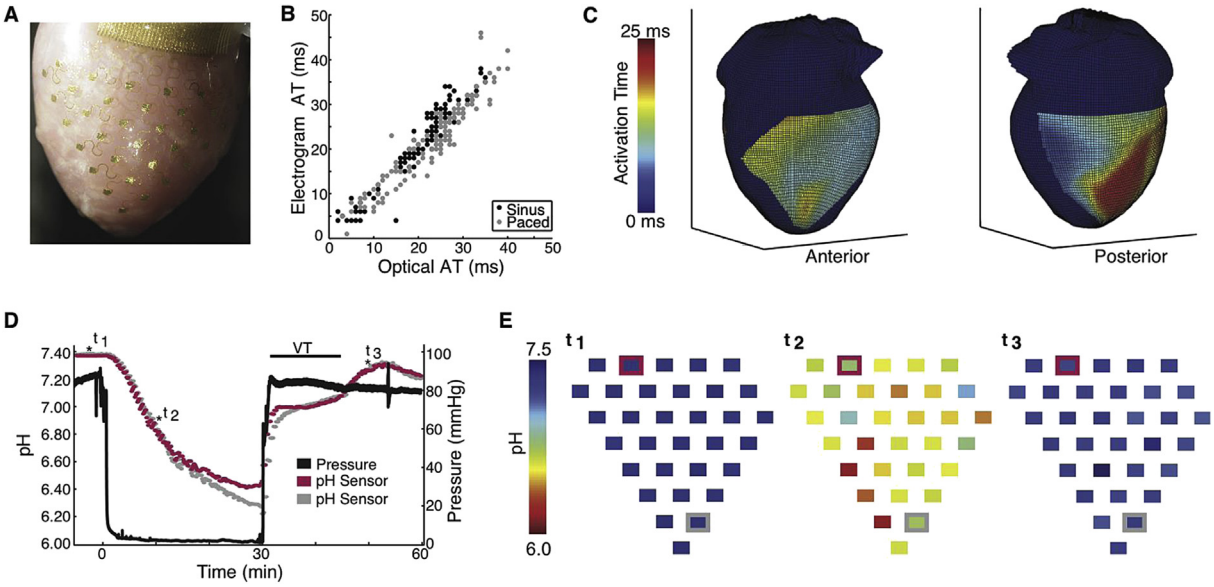


**Fig. 5. Diagnostic Application**. **A** Rabbit heart with gold sensors. **B** Comparison between electrical and optical activation times recorded simultaneously during pacing (2 Hz) and sinus rhythm. **C** Activation maps recorded from surface electrodes superimposed on 3D geometry of heart. **D** Temporal change in pH during 30 min of no-flow ischemia followed by 30 min of reperfusion. Asterisks t1, t2, and t3 correspond to spatial pH maps in E. E pH maps from the surface electrodes Parts of this figure are modified from Xu et al., 2014 VT-Ventricular tachycardia.

and far-field sensing. Another correlation that could be studied is the underlying propagation patterns that lead to fractionation of the electrograms and whether these regions are critical drivers of arrhythmias or collisions of passive waves.

### 2.2. pH mapping

pH is an established marker that provides rapid and accurate information on the metabolic state of cardiac tissue. Despite the fact that the basis for pH changes in disease states is well understood, monitoring these changes at high spatiotemporal resolution is challenging. High-resolution optical techniques have been employed to measure intracellular pH, but require administration of fluorescent dye (Nakanishi et al., 1990; Zhang et al., 2013b). The optical absorption of current intracellular pH dyes is <650 nm and thus they are not suitable with blood perfusion (Han and Burgess, 2010). In addition to optical techniques, researchers commonly monitor pH in the bulk environment of cell culture and ex-vivo tissue experiments using glass electrodes. Glass electrodes are rigid, bulky, and provide a single measurement channel, and thus are not feasible for high spatiotemporal mapping on a beating heart. Miniaturized pH sensors have previously been implemented on a bendable substrate, Kapton, and were composed of a well-known pH sensitive metal, $IrO_2$ (Marzouk et al., 2002, 1998). Integration of these sensors on a bendable substrate, however, limited the quantity of sensors and testing to papillary muscle preparations. The current integration of $IrO_2$ pH sensors into a flexible-stretchable substrate allowed high-density (32 sensors), real-time monitoring of pH on beating hearts.

To date, high-density pH mapping has been done on the epicardial and endocardial surface of explanted rabbit and donated human hearts during ischemia-reperfusion (Chung et al., 2014; Xu et al., 2014). Fig. 5D–E displays the change in pH on the left ventricular free wall of a rabbit heart during ischemia-reperfusion. At baseline, all pH sensors have values between 7.37 ± 0.03. The responses of two pH sensors are highlighted in grey and pink over the entire protocol, while the complete spatial pH maps (32 sensors) are shown at $t_1$ (prior to ischemia), $t_2$ (10 min into ischemia), and $t_3$ (20 min into reperfusion). Ischemia resulted in a slow decrease in pH, while reperfusion led to a rapid increase in pH that was halted at ~7.00 during an episode of ventricular tachycardia. Change in pH is simple to quantify especially compared to electrogram and ECG parameters and has a strong potential to provide clinicians with valuable information on the condition of the heart.

### 2.3. Light emitting diodes

Accompanying the sensors, these membrane devices can also be equipped with actuators. Light emitting diodes of a variety of wavelengths can be employed for optical spectroscopy of internal fluorophores and added fluorescent dyes. To date the UIUC group has created arrays of stretchable LEDs 300 μm × 300 μm in size ranging from 450 to 670 nm in wavelength. These LEDs are built by stamping aluminum indium gallium phosphide semiconductor materials into stretchable substrates and then sealing the circuit to ensure seamless operation in full submersion of physiological fluids (Kim et al., 2011c, 2010). With full spatial control over powering the LEDs, these devices can interrogate regional differences in fluorescence with targeted excitation. By pairing custom LEDs with stretchable silicon-based photodiodes (Khang et al., 2006) or miniature digital camera components (Song et al., 2013) researchers can use this technique for localized diagnostics of intrinsic fluorescent indicators like NADH, which has been demonstrated as an attractive biomarker in ex vivo studies (Asfour et al., 2012).

## 3. Potential therapeutic applications

In addition to the numerous diagnostic applications of these devices, there are also sensing and actuating capabilities that make them a relevant therapeutic tool. The same LED arrays can be used in spatially targeted optogenetics or the release of light-activated drugs. A protocol was recently published outlining the feasible use of these LEDs in a device designed for optogenetic studies in neuroscience (McCall et al., 2013). The wavelengths are already tailored for excitation of light sensitive channel Rhodopsin

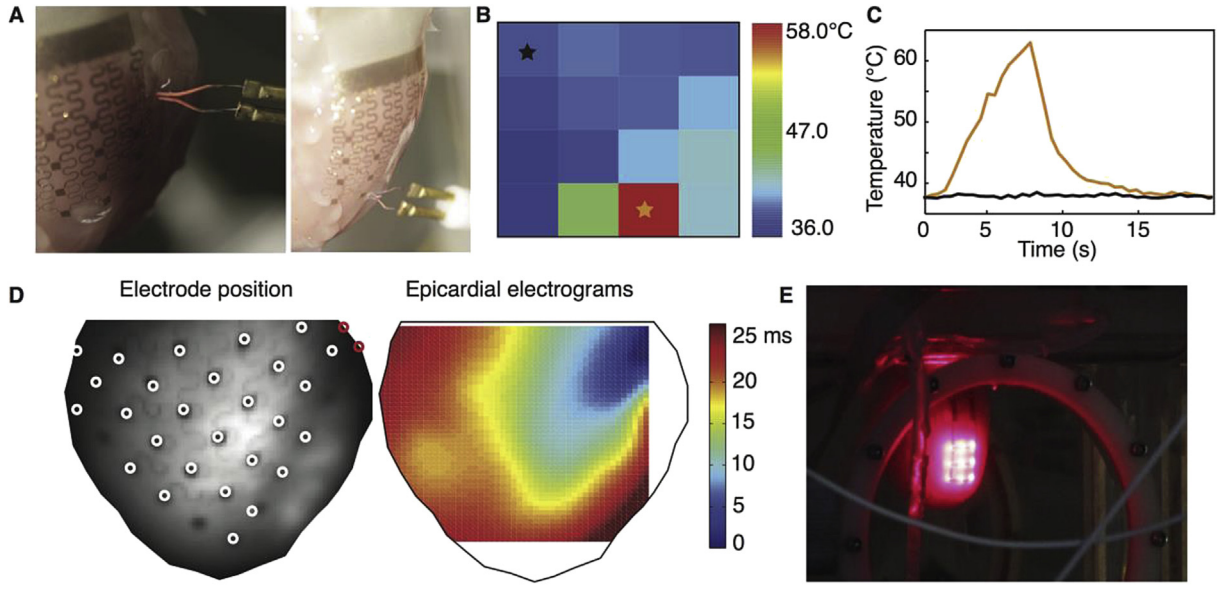


**Fig. 6. Therapeutic Application**. **A** Experiment simulating localized ablation. **B** Spatial temperature map showing increase in temperature near region of ablation (orange star) **C** Time traces of measured temperature at electrode near the site of ablation (orange) and far from it (black) **D** Activation map created from stimulating with bipolar pair of platinum electrodes and recording from the remaining 30 electrodes on the epicardial membrane. **E** 670 nm LED array on heart showing feasibility of light sensitive therapeutics. Parts of this figure are modified from Xu et al., 2014.

membrane receptors. The LEDs can also be paired with photodiodes to include feedback on the area that is receiving illumination. Using stretchable membranes in the place of fiber optics could provide an internal light source that does not impede physical behavior, a significant hurdle in in vivo optogenetic studies and eventual transition to clinical use of any therapy that relies on light.

Furthermore, incorporating these sensors in a number of clinical procedures could provide clinicians with much-needed feedback on the instantaneous effect of therapy. A great example of this would be to add a planar device with temperature and electrograms sensors to the epicardial surface during ablation procedures. The temperature sensors can help guide protocols for the duration and force applied to ablation catheters by measuring the increase in tissue temperature and the extent of tissue that has increased in temperature. Additionally the signal morphology of the electrograms can help identify regions of effective conduction block, equivalent to successful ablation lines. If these sensors were to remain on the patient's heart after the procedure, the device could alert the physician when a line of block recovers. The time course of recovery may help explain the mechanism of arrhythmia recurrence after ablation procedures and guide new ablation techniques that could circumvent this occurrence.

Another clinical therapy that might benefit from the addition of such a device is the use of stimulators and defibrillators. The square electrodes can be fabricated using platinum instead of gold for targeted pacing applications. Bipolar pacing has been achieved through these devices in the ex vivo rabbit heart (Fig. 6). New fractal structural designs can be implemented to build electrodes with greater surface area to deliver high voltage shocks without sacrificing the mechanical stretch (Fan et al., 2014). With a combination of sensing and shocking electrodes, a device could be conceived for high definition therapy, targeting only the spatially vulnerable regions as identified by the sensors instead of limiting the shock to a single vector. A defibrillation protocol that takes full advantage of the spatial coverage of the electrodes can be implemented to target arrhythmias with a potential decrease in peak voltage required to successfully defibrillate. Additional sensors including pH or ionic sensors can be added to instantaneously indicate myocardial injury due to high voltage shocks or reduce the number of inappropriate shocks.

## 4. Future advances

Flexible and stretchable multiplexed sensor devices are promising new tools for cardiac diagnostics and therapy. They offer the ability to design customizable arrays of sensors and actuators, using the aforementioned as well as others that are in the development stage including resistive strain sensors and ionic concentration sensors. Before chronic implantation of these devices is achieved, there are several remaining challenges to be faced. First, the wired connections must be replaced with full duplex wireless communication. Work has begun to incorporate RF transmitters (McCall et al., 2013) into similarly fabricated devices. Additionally, fatigue testing has to be performed to establish the lifetime of the serpentine wired circuit, which needs to withstand the stress of a heart beating ~30 million times per year. Future devices need evenly spaced sensors encompassing the entire heart surface. The complex shape of the atria, pulmonary veins, and great vessels make the development of atrial-specific devices difficult; however, the medical imaging techniques that provided the ventricular geometry can also be employed for the atria. Transitioning to *in vivo* feasibility studies would also require the development of a minimally-invasive deployment strategy. Previous experience with minimally invasive implantation methodologies used for ventricular assist devices, valves and pacemakers/defibrillators will be the basis for such future development, but significant improvements will be needed for deployment of high-definition future devices.

Continuing work on the substrate chemistry and material properties will also open doors for new applications. Energy requirements are a concern for electronically implanted devices, including pacemakers and defibrillators that rely on battery power for operation. Recently, piezoelectric energy harvesting and storage have been developed through flexible and integrated systems that use the natural motion of the beating heart as an energy source. Harvesting power directly from natural processes of the body is an attractive method to reduce battery size and eliminate the need to

replace them (Dagdeviren et al., 2014). In addition to energy harvesting, transient electronics is an emerging new area in material science that has numerous cardiac applications, such as the temporary monitoring of transplanted tissue constructs to ensure proper integration. Transient circuits are built with magnesium, tungsten, zinc, and iron, all of which dissolve in physiological fluids and can be patterned onto stretchable membranes in a similar manner to the sensors and actuators mentioned previously (Dagdeviren et al., 2013). The dissolving rates can be tuned by the addition of different metals and current circuits can remain stable and then disappear within a few hours to 20 days (Dagdeviren et al., 2014).

With future development, these membranes can be implemented as near-continuous monitors of cardiac function and provide necessary interventions as well as enhance current technology. Implantable defibrillators would benefit from comprehensive monitoring, where traditional low resolution electrical monitoring can lead to improper identification of arrhythmias and inappropriate, painful shocks to patients. Additionally, ablation therapy of atrial fibrillation relies on multielectrode basket catheters to locate ectopic foci or reentrant wavefronts with limited endocardial contact. Form-fitting, comprehensive diagnostic catheters could reduce the time to determine the electrical activation pattern reducing procedure time and improving patient outcomes. Combining the exciting new advances and the recent demonstrations in cardiac applications, customizable stretchable substrates for multiparametric sensors and actuators have the potential to greatly increase the amount of data available to clinicians and researchers studying pathophysiological disease states of the heart.

## Editors' note

Please see also related communications in this issue by Ambrosi et al. (2014) and Uzel et al. (2014).

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