MINIMALLY INVASIVE ELECTROCHEUTICAL CATHETER FOR ENDOLOGICAL DEFECT SEALING

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Surgical repair of lumen defects is associated with periprocedural morbidity and mortality. Endovascular repair with tissue adhesives may reduce host tissue damage, but current bioadhesive designs do not support minimally invasive deployment. Voltage-activated tissue adhesives offer a new strategy for endoluminal repair. To facilitate the clinical translation of voltage-activated adhesives, an electroceutical patch (ePATCH) paired with a minimally invasive catheter with retractable electrodes (CATRE) is challenged against the repair of in vivo and ex vivo lumen defects. The ePATCH/CATRE platform demonstrates the sealing of lumen defects up to 2 millimeters in diameter on wet tissue substrates. Water-tight seals are flexible and resilient, withstanding over 20,000 physiological relevant stress/strain cycles. No disruption to electrical signals was observed when the ePATCH was electrically activated on the beating heart. The ePATCH/CATRE platform has diverse potential applications ranging from endovascular treatment of pseudo-aneurysms/fistulas to bioelectrodes toward electrophysiological mapping.

INTRODUCTION

Luminal defects occur across blood vessels and range in severity from life-threatening (e.g., pseudo-aneurysms) to chronic events causing prolonged infections (e.g., arteriovenous fistula). Treatments nearly always rely on invasive open surgeries that risk more complications (1, 2). Advances in endovascular and transcatheter approaches minimize invasive risks but are limited to mechanical fixation techniques such as stents and metallic barb fixation of endografts. The mismatch of metallic and soft materials can erode soft tissues and lead to perforation and local inflammation (1–5). The replacement of rigid metallic tethering with flexible biomaterials is desirable, but the lack of on-demand tissue adhesives often necessitates traumatic anchoring with sutures or hooks, which causes additional mechanical trauma to the underlying tissues (6–8). Tissue adhesives and polymeric hydrogels have the potential to allow for atraumatic anchoring by providing stress distribution at the interface, but most existing designs are incapable of on-demand activation, especially with minimally invasive catheters. For example, (i) cyanoacrylate-based glues rapidly undergo anionic polymerization on nearby substrates in the presence of moisture, making them unsuitable for site-specific activation, (ii) fibrin-based sealers and other two-part adhesives are often viscous and require complex mixing chambers that prevent catheter incorporation or repositioning, (iii) on-demand ultraviolet (UV) curing adhesives/hydrogels require light intensities that can be higher than fiber optics can transmit, hence encounter optical challenges of minimum bend radius and isotropic scattering (9, 10). Cyanoacrylate glues have been previously reported for the closure of arteriovenous fistulas (6) but lack spatiotemporal activation and cannot be repositioned. Their fracture strength is higher than soft tissues that lead to tissue tearing during removal, unintended catheter fixation, and emission of toxic formaldehyde (11). Curing with UV light provides the end user with precise spatiotemporal control of the cross-linking procedure, recently exploited for the repair of arterial and ventricular defects and bleeding (12). However, UV exposure poses an engineering barrier for minimally invasive catheters. Light delivery to deep complex tissue structures is challenging and may result in curing gradients due to loss of transparency. Other embolic materials (polymeric coils or plugs) have also been reported for sealing of aneurysmal or luminal defects (6, 13). These polymeric coils or plugs may lead to downstream adverse effects such as implant migration and claudication (14, 15). One such polymeric material Onyx has been reported to cause vasospasm, endothelial necrosis, and risk of catheter entrapment at the injury site (13, 16).

One-part voltage-activated adhesives (also known as Voltaglue) are a relatively new platform of on-demand bioadhesives that rely on electrochemical cross-linking. Previous findings demonstrate that they adhere to biological tissues with similar viscoelastic material properties (17). Hypothesized carbene-mediated cross-linking, with diazirine as a precursor in Voltaglue, allows control over both thin-film implants (17–21). The in situ voltage cross-linking method permits the use of the Voltaglue in tissues that can be accessed through catheterization. Advancing voltage-activated adhesives for lumen defects such as arterial perforation, pseudo-aneurysms, or fistulas requires a catheter design that facilitates patch delivery and subsequent intraluminal cross-linking using electric current.

The engineering of such a transcatheter electroceutical device is herein broken into subcomponents: (i) ePATCH, a flexible...
two-electrode patch coated with Voltaglue, and (ii) CATRE, a minimally invasive catheter with retractable electrodes that transits the coiled ePATCH to the lumen defect and deploys it via balloon inflation. The reported technology provides a new tissue/implant interface that adheres to wet tissues, matches the material properties of tissues, supports seamless integration over dynamic tissues, and delivers on-demand biomaterials in situ. The engineering and demonstration of the ePATCH/CATRE system on ex vivo porcine lumen defects are presented as a flexible platform system that can be tailored for potential electroceutical implants encompassing bioagent delivery, tissue repair, diagnostics, or a combination thereof.

RESULTS
Scope and study design
Voltage-activated biomaterials have been previously reported for their ability to adhere to tissues but lack a minimally invasive delivery system (17, 18). Here, an endoluminal electroceutical catheter is designed that can deliver voltage-curable adhesives and propagate electric voltage to adhere thin-film patches onto lumen defects. The electroceutical catheter consists of two subcomponents: ePATCH and CATRE. ePATCH is a flexible graphene electrode patch coated with bioadhesive (i.e., Voltaglue), and CATRE is a minimally invasive balloon catheter with retractable nitinol wire electrodes. ePATCH is constructed by three-dimensional (3D) printing graphene inks (22) on electrically insulating, biocompatible, and impermeable polymer substrates. CATRE is designed to navigate tortuous anatomies endoluminally, transport and deploy a coiled ePATCH via balloon inflation, and deploy electrical leads that subsequently retract after Voltaglue activation. For minimally invasive surgical interventions in vessel lumens ranging from 7.5 to 30 mm, CATRE was designed within an insertion size of 7 mm (~21 French), an elastomeric balloon with an expanded diameter of 10 to 30 mm (at 5- to 20-atm pressure), and a flexible shaft with radiopaque markers for fluoroscopic navigation (23).

Structure-activity relationships of the electroceutical catheter tested at three current levels (1, 2, and 3 mA) were evaluated against viscoelastic material properties via a rheometer. The repair of lumen defects with the electroceutical catheter platform was modeled with defects and subsequent closures on the porcine aorta, carotid artery, and epicardium. In vitro lap shear, burst pressure, and wound closure tests were benchmarked to a commercially available arterial, and epicardium. In vitro lap shear, burst pressure, and wound closure tests were benchmarked to a commercially available artery, and epicardium. In vitro lap shear, burst pressure, and wound closure tests were benchmarked to a commercially available artery, and epicardium. In vitro lap shear, burst pressure, and wound closure tests were benchmarked to a commercially available surface/tissues (Fig. S1). The resulting thin films are referred to as an “electrode patch” throughout the text. A thin layer (~500 μm) of Voltaglue is spread over the electrode patch, and the resulting assembly is referred to as “ePATCH” throughout the text. Conductive graphene ink (800 S m⁻¹) provides dry adhesion on collagen, cellulose, thermoplastic elastomer (TPE), Medtronic silicone sheets, and SurgiWrap [70:30 poly(lactide-co-d, l-lactide)] sheets. The electrode patch allows the current to pass through Voltaglue. Cross-linking chemistry before and after activation of the ePATCH with the CATRE describes the carbene insertion into the nearby surfaces/tissues (Fig. 2A). Uncured Voltaglue is a viscous aqueous polymer that can be easily spread over a surface. Real-time rheological investigations confirm the viscous behavior of the adhesive (Fig. 2B, i). Before curing, the loss modulus (G″) is higher than the storage modulus (G′).
Exposure to electric current facilitates cross-linking that increases the storage modulus and transforms Voltaglue into a viscoelastic film. The electric current of three different magnitudes (1, 2, and 3 mA), below the range of physiological let-go current (≤5 mA) (25), was evaluated to maximize the storage modulus. The maximum voltage versus time plot shows an increase in the maximum voltage with time, indicating that electrocuring increases the resistance of Voltaglue (fig. S6). The ePATCH with no external electric current served as a control. Any rise in $G'$ and gelation were not observed in the case of control (no electric current, no cross-linking expected). Storage modulus ($G'$) directly correlates, whereas gelation time (the time point when $G' = G''$) inversely correlates with electric current (Fig. 2B, ii and iii). Rapid gelation is achieved within 20 s for 3-mA curing conditions, but this requires the highest voltage.

**External electric current/voltage does not leak into nearby tissues**

Voltaglue can be activated with both DC and AC (17–19). A DC of 200 to 300 mA passes through the human body without harmful effects, but even an AC of 30 mA can cause an abnormal heart rhythm (26, 27). Considering the characteristics of the electrical current and safety concerns, DC stimulation is chosen. The DCs applied are relatively small (1 to 3 mA), but as a precautionary measure, the leakage of applied electric current from the electroceutical catheter into nearby soft tissues is investigated with COMSOL Multiphysics, and the simulations are compared with experimental results. Figure S5 shows a 3D schematic of the tissue/ePATCH interface. The $z$-plane multislice results of finite element modeling illustrate the surface distribution of electric voltage across the patch (Fig. 2C, i). The surface electric potential is maximum at the cathode and decays gradually toward the anode. This simulation matches the experimental results where the activation initiates at the cathode and progresses toward the anode, as visually observed through nitrogen generation (movie S1). The 2D finite element modeling of the electric field demonstrates that the electric field lines penetrate only up to a depth of 1 mm in the nearby tissues upon stimulation by a current of 2 mA. The simulated ePATCH exhibits a surface electric potential of 3 to 4 V (Fig. 2C, i), whereas the experimental stimulation of ePATCH requires a voltage range of 3 to 100 V (Fig. S6). The mismatch is attributed to the varying resistance of the
Fig. 2. Voltage-curable bioadhesives and curing kinetics. (A) Chemical structure of voltage-activated adhesive (also known as Voltaglue) before and after exposure to electric current. The digital images display the activation of the ePATCH via CATRE. (B) Real-time rheological properties of electrocured Voltaglue. (i) Representative real-time storage ($G'$) and loss ($G''$) modulus before and after 1-, 2-, and 3-mA electric current stimulation. (ii) Maximum $G'$ after the termination of electric current following 8 min. Control, no current applied. (iii) Gelation time ($G'' = G'$) versus electric current applied. (C) The exogenous electric field in the vicinity of soft tissues. (i) Finite element modeling in COMSOL Multiphysics, illustrating the distribution of electric voltage over the surface of the ePATCH. (ii) Schematic of the tissue/ePATCH assembly designed to test the leakage of the electric current into the nearby tissues. (iii) Stray electric currents recorded by an ammeter in the porcine heart tissues with and without stimulation of the ePATCH in the vicinity. Data are presented as means ± SD, $n = 3$, and $P$ values are calculated using one-way analysis of variance (ANOVA) with Tukey correction, $*P < 0.05$. NS, not statistically significant. Photo credit: Manisha Singh, NTU.
Repair of lumen defects in soft tissue ex vivo and in vitro models

For visual identification of the electroceutical catheter process and to assess whether ePATCH can adhere to synthetic materials, a transparent polyvinyl chloride (PVC) tube with a 2-mm defect was used to mimic a damaged vessel lumen (Fig. 3A). Briefly, the procedural steps are as follows: insertion of the catheter to the defect site, balloon inflation to position ePATCH over the lumen defect, activation of Voltaglue via the nitinol cathode (−) and anode (+), and retraction of the nitinol shape memory wires upon successful closure of the defect (movie S2). In addition, an ePATCH was deployed and adhered inside a porcine aorta attached to whole excised porcine hearts in a physiologically relevant assembly. Two endoscopic cameras were used to guide the catheter to the aorta (Fig. 3B). This required CATRE to navigate a bend radius of 20 mm to navigate to the aortic defect site, indicating that the catheter can navigate through typical aortic anatomy (29). The ePATCH remained attached and coiled around the balloon, even in the absence of a protective sheath, demonstrating the flexibility and robustness of the CATRE/ePATCH design through complex organ structures (movie S3). Porcine aorta branching from an ex vivo heart serves as a model defect location, chosen because of its importance in diagnosing aortic valve regurgitation (e.g., aortic valve stenosis). Another vascular defect closure procedure was performed in the aorta connected to an in vitro mock circulatory loop (Fig. 3C). The 2-mm defect size was created as per American Society for Testing and Materials (ASTM) F2392-04, which is a clinically relevant model for a standard test method for burst strength of surgical sealants. CATRE was navigated toward the defect site and ultimately secured ePATCH to the intraluminal wall of the defect.

The adhered patch must withstand the hoop stresses exerted by the blood pulses inside the vessels. Normal physiologic levels of shear stress within arteries range from 0.001 to 0.007 kPa, whereas shear stress in veins ranges between 0.0001 and 0.0006 kPa in vivo (30). Shear adhesion strength at failure is an indication of the substrate-dependent shear forces against collagen films, porcine aorta, and porcine heart (Fig. 3D, i). The shear adhesion strength of Voltaglue ranged from 10 to 60 kPa, which is 10^5 times higher than arterial and venous shear stresses. Voltaglue shear adhesion strength is compared favorably to DuraSeal, which provided a shear adhesion of 3 to 10 kPa on the same substrates (Fig. 3D, ii to iv). Voltaglue demonstrated significantly higher lap shear adhesion strength than commercially available DuraSeal sealant on wet tissue substrates (P < 0.05).

After the lap shear tests, the freeze-dried tissue specimens were cross-sectioned and assessed for the mechanism of failure and the nature of adhesive fixation. Scanning electron microscopy and Masson’s trichrome (MT) staining of the interface allowed for demarcation of Voltaglue and an expanded analysis of lumen defect sealing. Voltaglue conformally bonds to the intima layer of the aortic tissues (Fig. 3E). Failure analysis of the Scanning electron microscopy cross section suggests cohesive failure and no underlying damage to the tissues. MT staining in Fig. 3F shows that the expansion of Voltaglue seals the defect site via a plug that extends from the lumen interior (inferior) to the lumen exterior (superior). The expansion results from (i) Voltaglue foaming via N₂, (ii) pressure applied by the inflated balloon, or (iii) a combination thereof (movie S1).

Repair of an ex vivo fistula on porcine renal artery

A minimally invasive technique for addressing fistulas (e.g., vesicovaginal, tracheoesophageal, or arteriovenous fistula) is an unmet medical need (24). Arteriovenous fistulas are prioritized targets for endovascular repair, but existing two-component bioadhesives are too viscous to traverse narrow catheter channels that are often less than 1 mm. Voltaglue and its design within the CATRE/ePATCH may circumvent these impediments for sealing of arteriovenous fistulas attached to major arteries or veins. Porcine arteries and synthetic vascular grafts served as ex vivo and in vitro arteriovenous fistula models (Fig. 4, A and B). Key steps in the fabrication and assembly of the ex vivo and in vitro fistula models appear in Material and Methods. These engineered fistula models are representative of two different vascular procedures—graft surgeries use autologous vessels (e.g., thoracic artery) for small-diameter vessels (<6 mm) and synthetic vascular grafts for large-diameter blood vessels (>6 mm) (31). A miniaturized CATRE (fig. S4) repairs the ex vivo renal fistula site by delivering and activating the ePATCH over the 2-mm bifurcation (Fig. 4A). The fistula sealing procedure in the in vitro vascular graft fistula model demonstrates the capability of the ePATCH to bond with synthetic graft materials (Fig. 4B). This may have additional clinical implications as vascular grafting is a routine procedure and Voltaglue can expand in the uneven, coiled troughs (depth, ~500 μm) of vascular grafts. The adhesion strength of the ePATCH against the vascular graft is 28 kPa as characterized by lap shear testing (Fig. 4C), which is ~5 times higher than a commercially available Fibrin sealant used in graft surgeries (32).

To investigate leak-proof sealing of the fistula defect, we connected the ex vivo and in vitro models (before and after fistula sealing) to a pressure feedback assembly (Fig. 4D, i) via Luer locks. The hydrostatic pressure of 225 mmHg was applied from a pressure source (mimicking arterial hypertension), and the leaking pressure was measured by a pressure sensor across the vein mimic arm to test ePATCH adhesion. The drop of pressure to ~5 mmHg demonstrates a firm sealing of the fistula defect (Fig. 4D, ii and iii). Burst pressure evaluates ePATCH’s sealing of tissue defects subjected to fluidic pressure on wet substrates of collagen sheets,
Fig. 3. Proof of concept of the CATRE demonstrating the closure of lumen-associated defects in tubular structures ex vivo and in vitro. (A) In vitro closure of an artificially created intraluminal defect in PVC tube. (B) Proof of concept of device functionality to adhere ePATCH at a blind site on porcine aorta luminal wall. (C) Proof of concept of the device feasibility on closing a 2-mm defect in the porcine aorta connected to a mock circulatory loop. (D) The lap shear adhesion strength of ePATCH adhered to different biological substrates using an electric current of 1 to 3 mA. Control, DuraSeal—a commercially available sealant. (i) Schematic of the lap shear test assembly. (ii) The maximum shear adhesion strength at failure against collagen sheets. (iii) The maximum shear adhesion strength at failure against porcine aorta. (iv) The maximum shear adhesion strength at failure against porcine heart. (E) Interaction between the activated Voltaglue and porcine aorta as observed under a scanning electron microscope (SEM). T, tissue; B, bioadhesive aka Voltaglue. (F) Cross section showing the interface of the ePATCH against a porcine carotid artery as evaluated ex vivo through Masson’s trichrome (MT) staining. P, graphene electrode patch. MT staining colors the Voltaglue/ePATCH red and the tissues blue. The defect is that the artery is sealed using miniaturized CATRE. Data are presented as means ± SD, n = 3, and P values are calculated using one-way ANOVA with Tukey correction, *P < 0.05. Photo credit: Manisha Singh, NTU.
Fig. 4. Demonstration of potential clinical applicability of CATRE in sealing a fistula ex vivo and in vitro. (A) Proof of concept of arteriovenous fistula defect closure in an ex vivo model created by adjoining the renal and carotid porcine arteries for vessels with <6 mm in diameter. (B) Proof of concept of arteriovenous fistula defect closure in an in vitro model produced by adjoining two vascular grafts with a diameter of 20 and 10 mm, mimicking the vessels with >6 mm in diameter. (C) The lap shear adhesion strength of the ePATCH against the vascular graft at electric currents of 1 to 3 mA. Control, no current applied. (D) Testing of a leak-proof sealing of the fistula defect. (i) Schematic of the custom-made pressure feedback assembly. A pressure of 225 mmHg is applied from the source and measured by the pressure sensor connected at the end of the vein-mimicking arm. (ii) Pressure sensed by the pressure sensor before and after the sealing of the fistula in an ex vivo artery-based model. (iii) Pressure sensed by the pressure sensor before and after the sealing of the fistula in an in vitro vascular graft–based model. (E) Burst pressure test. (i) Schematic of test setup to evaluate the burst pressure of the ePATCH after stimulation with 1- to 3-mA electric current. Control, DuraSeal—a commercially available sealant. (ii) The average burst pressure of the ePATCH against collagen sheets. (iii) The average burst pressure of the ePATCH patch against porcine aorta. (iv) The average burst pressure of the ePATCH patch against porcine heart. Data are presented as means ± SD, n = 3, and P values are calculated using one-way ANOVA with Tukey correction, *P < 0.05. Photo credit: Manisha Singh, NTU.
porcine aorta, and porcine heart (Fig. 4E). The burst pressure of the ePATCH against collagen increased from 150 to 225 mmHg and 350 mmHg with increasing electric current. The burst pressure of the ePATCH against the porcine aorta and heart reached a maximum value of 150 and 90 mmHg, respectively. Voltaglue provides up to ~2.3 times higher burst pressure than commercially available DuraSeal sealant against aortic tissues.

**Electrocured ePATCH can withstand physiological pressures under pulsatile flow**

The usage of CATRE for endovascular procedures, e.g., reinforcement of aortic dissections (Fig. 5A) creates a risk of Voltaglue washout during catheter navigation that may compromise ePATCH deployment. To test for this, we submerged porcine carotid arteries with a 2-mm defect in heparin-infused porcine blood. The miniaturized CATRE navigates to and seals the defect of the injured carotid artery with the ePATCH. Voltaglue plugs the defect transmurally as shown by hematoxylin and eosin (H&E)—stained carotid arteries (Fig. 5B), demonstrating that blood presence does not compromise the performance of the electrocatheter.

Synthetic materials pose the risk of inducing platelet activation and subsequent clotting when in contact with blood or platelet-rich plasma. Platelet attachment testing via a lactate dehydrogenase (LDH) assay determines the thrombogenic potential of the Voltaglue, graphene electrodes, and biocompatible substrate (Fig. 5C). DuraSeal sealant and UV-cured Voltaglue (33, 34) were used as a control. The platelet adhesion of Voltaglue (both cured and uncured) is not significantly different from DuraSeal control. The biocompatible substrate exhibited 95% less platelet adhesion than DuraSeal. The backing substrate of ePATCH comes into direct blood contact and displays the lowest thrombogenic potential. The thrombogenic nature of the other ePATCH components accelerates the sealing of the perforated defect.

An aortic leak sealing procedure demonstrates the capacity of the CATRE to close a 3-mm defect on the porcine aorta under a continuous flow of citrate-infused porcine blood (Fig. 5D). For proof of concept, the blood was pumped in the direction of the red arrow at a rate of 10 ml min⁻¹ through the aorta connected to an in vitro mock circulatory model (movie S4). Upon defect sealing, the catheter was removed, and the ePATCH was retained for ~1000 physiologically relevant stress/strain cycles before the aorta was spliced to reveal successful adhesion of the patch over the artificially created defect.

To check the ability of adhered ePATCH to withstand the physiological pulsatile pressure and shear stresses inside a lumen, a blood mimic fluid [apparent shear viscosity of 3 centipoises (cP)] was pumped at 2 liters min⁻¹ in a circuit housing a pulsatile pump, a pressure sensor, a fluid reservoir, and a compliance chamber (fig. S7). A collagen tube with a diameter of 3 cm that mimics the aorta was connected to the circuit, and pulsatile pressures similar to physiological pressure (60 to 125 mmHg) were applied (Fig. 5E). Three 2-mm defects were created in the collagen tubing with pressure continuously recorded in real time. The differential pressure dropped by 18% with these defects compared to intact collagen tubing. After sealing the three defects with the ePATCH, the pressure was continuously monitored within the pulsatile flow circuit. The sealed lumen regained the physiological pressure range, and Fig. 5E (ii) demonstrates physiological pressures over 5 hours after sealing. The clinically pertinent results exhibit water-tight, flexible, and robust adhesion to wet substrates for over 20,000 physiologically relevant dynamic stress/strain cycles.

**Effects of electrocuring voltages/current on tissues in vivo**

To assess the high voltage effects on the internal physiology, we used the modified miniaturized catheter to electrocure the ePATCH in vivo directly on the most electrically sensitive organ, i.e., a live beating heart in rats (Fig. 6A). Voltaglue was activated using modified CATRE under wet and dynamic conditions for 5 min at 3 mA on the rat’s epicardial surface. The maximum ex vivo adhesion strength of ePATCH obtained against the rat’s heart was ~12 kPa as measured by the lap shear test (Fig. 6B). This exceeds the adhesion strength provided by Fibrin glue (~5 kPa) in vivo (32).

A lead II electrocardiogram (ECG) recorded the electrical activity of the heart in real time during the electrocuring (Fig. 6C). The R-R intervals before, during, and after electrocuring were 221 ± 1.7, 205 ± 2.3, and 206 ± 0.97 ms, respectively, which lie in the range for normal matured rats (118 to 251 ms) (35). A professional pathologist examined the histological sections (sample blinded) of the explanted rat hearts and concluded that histological changes in the heart are only seen in the epicardium and not associated with any inflammatory cell infiltrate (Fig. 6D). This could represent damage to the epicardial tissue before the influx of inflammatory cells as part of response and repair to tissue damage; however, there are no substantial pathological changes present within the underlying myocardium layer, as well as in the endocardium layer, and these appear within normal limits.

Tack adhesion strength tests the ability of ePATCH to adhere to the epicardial surface of freshly excised pig hearts (Fig. 6E). A custom-designed jig immobilized the whole heart to the lower clamp of the mechanical tester (Fig. 6E, i). Tack adhesion strength ranged from 5 to 10 kPa, which is 80 to 90% stronger than commercially available DuraSeal sealant (Fig. 6E, ii). Tack adhesion was used to evaluate the capacity of Voltaglue to bond to the porcine aorta and collagen films. Voltaglue reached its maximum adhesion strength of 14 kPa against aorta and 40 kPa against collagen at an electric current of 3 mA. For similar curing times of 5 min, the ePATCH against aorta and collagen is about 300 and 700% stronger than a commercially available DuraSeal sealant (Fig. 6E, iii and iv). The relatively weaker adhesion of Voltaglue on natural tissue surfaces than synthetic materials may be attributed to the hydrated proteoglycans on tissue surfaces, fouling carbene insertion.

**DISCUSSION**

Lumen defects range from acute microperforations to chronic transmural leaks and are associated with most tubular internal organs. Vascular perforation, blunt thoracic aortic injuries, intramural hematomas, and aortic pseudo-aneurysms are some examples of lumen defects in need of repair options. Sutures and metallic coils remain the best available means for lumen defect closure. Polymeric glues (e.g., cyanoacrylates and fibrin sealants) are available, but cyanoacrylates are contraindicated for internal use, and fibrin sealants are relatively weak hydrogels. UV-activated hydrogels pose a risk of skin curing due to loss of transparency. While there are strategies to overcome the “skin curing effect” such as the use of photoinitiators with wavelengths that shift away from the UV wavelength after activation or have enough efficiency/amplification to allow full cross-linking of the material (36), there are limitations
related to premature photoinitiator dissolution or necessitating high doses of photoinitiators that can have cytotoxicity concerns.

Voltage-activated (also known as Voltaglue) adhesives bond to wet tissues and nearby polymer surfaces under on-demand application of the external electric field (17–20). This requires a mechanism for transcatheter delivery and activation. While the catheter manufacturing in the laboratory settings is not as sophisticated as that demonstrated in industry, the results herein give a working design toward endovascular delivery of voltage-activated bioadhesives and elastic films for lumen defect closure. The electroceutical lumen repair device engineered consists of two main components—(i) ePATCH, the thin, flexible adhesive patch; and (ii) CATRE, minimally invasive balloon catheter. The ePATCH can be further divided into three subcomponents—(i) Voltaglue, voltage-activated bioadhesive; (ii) graphene electrodes, cathode and anode made up of nonmetallic, conductive ink; and (iii) biocompatible substrate, flexible, elastic, and an electrically insulating thin film. ePATCH adheres over a lumen defect by activation of Voltaglue, and CATRE transports the ePATCH under pulsatile pressures of physiological range (60 to 125 mmHg). Three defects of 2-mm diameter each are closed with the catheter device. (ii) Pressure readings in the collagen tube demonstrating pulsatile flow before defect creation, immediately after closure, and 5 hours after closure. Data are presented as means ± SD, n = 3, and P values are calculated using one-way ANOVA with Tukey correction, *P < 0.05. Photo credit: Manisha Singh, NTU.
Fig. 6. Effect of electrocuring voltages/current on a rat’s heart. (A) Surgical procedure showing activation of the ePATCH on the rat’s heart using the modified miniaturized catheter device. (B) The ex vivo lap shear adhesion strength of the ePATCH against the rat’s heart at electric currents of 1 to 3 mA as activated by the electroceutical catheter. Control, no current applied. (C) Representative lead II ECG recordings before, during, and after electrocuring. (D) Representative H&E-stained histological images of the explanted hearts in response to the electric current applied by the device during in vivo electrocuring. (E) The tack adhesion strength of ePATCH adhered to different biological substrates using an electric current of 1 to 3 mA. Data are presented as means ± SD, n = 3, and P values are calculated using one-way ANOVA with Tukey correction. *P < 0.05. Control, DuraSeal—a commercially available sealant. (i) Illustration of the tack adhesion test assembly. (ii) The maximum tack adhesion against the whole porcine heart. (iii) The maximum tack adhesion against porcine aorta. (iv) The maximum tack adhesion against collagen sheets. Photo credit: Manisha Singh, NTU, and Claudia E. Varela, MIT.
For clinical interfacing, CATRE navigates through a guidewire or guided endoscope cameras where guidewires are not preferred, e.g., gastrointestinal tracts. The entire procedure can be performed in two steps—(i) insert and inflate at the target site and (ii) activate, deflate, and retract from the body. The cohesive failure of the adhesive allows for failsafe removal to prevent stripping epithelial or endothelial cell layers.

Other intraluminal modalities for the closing of vascular defects have been reported previously. For example, Zenith Alpha stent-graft addresses blunt thoracic aortic injuries via an endovascular approach (37). These devices rely on the available fixation technologies such as metallic hooks and tines that perforate soft tissues (38). Another endovascular platform involves coil embolization with metallic wires until the defect sac is full (39). Coil embolization uses a metallic coil that leads to an artifact and scatters on repeat computed tomography imaging, making it difficult to assess the postsurgical treatment. The proposed CATRE/ePATCH platform offers an alternative soft tissue fixation approach for endoluminal defect closure. The viscoelastic nature of cured Voltaglue (approximately kilopascal) allows for an intimate, conformal wrapping against the soft, dynamic tissue surfaces. For example, the voltage-activated adhesive can attach the ePATCH against relatively smooth aortic tissues and uneven luminal surfaces of synthetic vascular grafts. This is relevant for soft-tissue applications where it is best to avoid tissue compression and stress concentrations that erode soft tissues.

To evaluate the catheter’s potential for in vivo application, we challenged it under real-world scenarios—navigation through tortuous structures of a swine heart, electrocuring on a live beating heart, and repairing defects in swine aorta. The conventional balloon-based design of the catheter allows for pressure-controlled inflation for various diameters (e.g., aorta, carotid arteries, renal arteries, intestines, etc.). CATRE offers a bend radius of 20 mm, thus easily maneuvered through large lumen vessels (10 to 30 mm), for example, the medium diameter of curvature of the aorta is 56 mm (29). ePATCH, when deployed with CATRE, is also evaluated for bonding biological tissues (e.g., porcine aorta and heart) under lap shear, tack adhesion, and burst pressure test methods. Electro cured Voltaglue required a higher maximum load at failure as compared with the DuraSeal sealant. ePATCH can also withstand physiological systolic pressure of up to 120 mmHg when bonded to the aorta intima. Voltaglue provides four times stronger shear adhesion and six times stronger tack adhesion than commercially available DuraSeal sealant against porcine aorta. Because of its viscous properties, the uncured Voltaglue exhibited minimal surface washout upon exposure to blood flow. The adhered ePATCH can withstand systemic pulsatile pressures ranging from 60 to 125 mmHg, as tested for 5 hours (equivalent to over 20,000 stress/strain cycles). This has implications for the preclinical application of the catheter device in transmural defect closures. MT- and H&E-stained images demonstrate that Voltaglue covers and plugs through the defect, which is attributed to the foaming nature of Voltaglue. This may be exploited in future designs for sealing small defects without the patch-assisted closure, suggesting the catheter design can be simplified by printing the electrodes directly on the balloon. Foaming is generated because of the evolution of N₂ gas as a by-product of electrocuring, but the released content is on the order of 0.1 cm³, and it is known that 200 cm³ nitrogen can be removed without causing any pathology-related concerns (40).

Because of its construction with electrically conductive components, combined with its conformability and antitraumatic properties, we envision that our catheter-based platform can be expanded within the emerging fields of flexible electroceuticals and biointegrated electronics such as diagnosing and monitoring of physiological vitals, for example, electrophysiological mapping, intraluminal pressure, and temperature sensing (41–45). CATRE/ePATCH has the potential to be further engineered to provide sophisticated multifunctionality (e.g., sensing and actuation), similar to those described in recent publications (46). Current electroceuticals rely on arrays of passive metal electrodes/sensors that target nearby soft tissues for recording and stimulation of electric signals (47, 48). The rigid nature of some metallic sensors prevents conformal contact with topologically demanding soft tissues (47–49). Soft, flexible circuits promise a better alternative to achieve intimate contact for emerging electroceutical systems (49, 50).

The components of the CATRE/ePATCH platform can be independently modified/substituted for ease of application design. For instance, Voltaglue can adhere to a variety of synthetic and natural substrates—TPE, collagen, poly-L-lactic acid, cellulose, porcine myocardium, swine aorta, porcine carotid artery, swine epicardium, and rat’s pericardium. Voltaglue can, however, be replaced with other voltage-activated adhesives (e.g., catechol and ferrocene-based), if nonfoaming, nonaqueous, or reversible cross-linking–based formulations are desired (51–53). However, the current formulations of catechol lack shelf stability when compared to Voltaglue. The electrically conductive patch required to interface the electric current to Voltaglue is made up of graphene ink composite. This ink is chosen because it is partially biodegradable, as it is formulated with 30% degrading polyester [poly(lactic-co-glycolic acid)] but substitutes abound such as conductive polymers of poly(3,4-ethylenedioxythiophene) polystyrene sulfonate or polyaniline (22, 54, 55). Activation of Voltaglue was first reported using commercially available three-electrode circuits, but, herein, a simplified two-electrode design is used. The three-electrode circuits for Voltaglue activation have the advantage of maintaining a constant voltage with a simple potentiostat, but their plastic designs cannot be translated to clinical applications. Similar two-electrode, graphene interdigitated electrodes also activated Voltaglue, with positive attributes of flexible, biocompatible components, but the activation was limited to the cathode and would require polarity switching to activate the complete surface, which is part of our future work (17, 18). The most recent evaluation with semiconducting surfaces demonstrated the activation area on the order of square centimeters but required relatively high-voltage electric fields of >2 V mm⁻¹. The current design of the ePATCH incorporates a dual-electrode geometry that optimizes the cathode area for DC activation, with sufficient surface area essential to seal 2- to 3-mm lumen defects. The flexible biocompatible substrate for the graphene electrodes can be biodegradable, leaving behind no permanent synthetic implants (e.g., SurgiWrap). For a permanent implant fixation application, the biodegradable patch can be easily replaced by a nondegradable patch (e.g., Medtronic ENT silicone sheets). For the thoracic aortic work, ePATCH of 0.5- to 1-cm size may not treat intramural hematoma or transection injuries, but it can be upsized via 3D extrusion printing. The electrocuring via ePATCH can be modified by changing the dimensions of the surface area. However, the design of the ePATCH may need to be modified to reach the required current densities per square millimeter.
This work is limited to proof-of-concept demonstrations of the technology and needs further design optimization before in vivo deployment or clinical testing. Some limitations of the device are noted. First, we used an electrocuring time of 5 min for ePATCH in vivo, which would not be suitable in vivo, especially if the catheter blocks blood flow. This was a conservative activation time and could likely be reduced. Future designs will also address activation without stopping the blood flow and further optimization of the gelation time to minimize blood flow disruption. Existing commercially available balloon catheters (e.g., Dispatch catheter) (56), as well as those described in the patent literature (57), can avoid restrictions in blood flow. Reduction of gelation time has been a focus of concurrent investigations through (i) optimization of AC-based stimulation of Voltaglue, (ii) Li⁺ cation-based Voltaglue formulations, and (iii) optimal temperatures (18). Another limitation of the current design is the overall size of the device. The current scope (with miniaturized device) is limited to the defect sealing in lumens with a diameter of 5 mm or above. The existing CATRE requires four lumens but can potentially be reduced to three by replacing the cathode and anode leads within a coaxial cable for navigation into smaller lumens (e.g., peripheral arteries). Future work will focus on advancing the design for clinical therapies. For example, (i) the catheter design with a detachable anode could further miniaturize the catheter profile and improve the size-to-performance ratio, and (ii) an antifoaming coating on the catheter would restrict the in vivo infection risks (58). However, all the materials used for the catheter technology are bioresorbable, but evaluating the long-term inflammatory effects on tissues with ePATCH material is also a part of our future work. For example, the thrombogenicity of the ePATCH at the time of insertion and over time until it is resorbed completely and afterward needs to be evaluated. While the platelet adhesion gives positive preliminary data, survival models will need to assess for long-term thrombus formation. In addition, long-term in vivo testing with large animal models (e.g., Porcine, n = 5 to 10) will be required before human translation. In addition, the adhesion strength and mechanical properties of the ePATCH further need to be optimized to improve its efficacy in cases of sustained hypertension with a blood pressure of >180 mmHg. Exploring and incorporating the Li⁺ cation-based Voltaglue formulations that have previously shown improved material properties (18) may address this limitation.

Here, we present a catheter-based technology that can deliver voltage inside body tissues to facilitate the on-demand, in situ cross-linking of biomaterials by electric current, enabling a new paradigm for transcatheter on-demand bioadhesive voltage activation. The system architecture and device design have the potential to advance a diverse array of minimally invasive surgical and diagnostic tools that can be used to activate adhesives for multiple clinical applications including vascular perforation, blunt thoracic aortic injuries, intramural hematomas, aortic pseudo-aneurysms, and arteriovenous fistula defects, all of which can potentially be addressed using multifunctional, intraluminal, voltage-delivering balloon catheter devices.

**MATERIALS AND METHODS**

**Synthesis of the voltage-activated bioadhesives (i.e., Voltaglue also known as PAMAM-g-diazirine)**

Generation 5 PAMAM (PAMAM-G5) dendrimer was purchased from Dendritech Inc., USA. 3-[4-(bromomethyl)phenyl]-3-(trifluoromethyl)-diazirine, referred to as aryl-diazirine throughout the text, was acquired from TCI, Japan. PAMAM-g-diazirine was synthesized with a 20% grafting ratio of aryl-diazirine onto the 128 surface amine groups of PAMAM-G5, as previously published (17–21, 51, 52). The synthesized PAMAM-g-diazirine (20%) was dissolved in phosphate-buffered saline (PBS; 1×) as a 50% (w/w) ratio, and the resulting viscous formulation is referred to as Voltaglue throughout the text.

**Fabrication of dual electrode patch**

3D graphene ink was purchased from Dimension Inx, LLC, USA. Graphene electrodes were printed using a CELLINK BIXO printer on a variety of bioresorbable and biocompatible substrates, for example, collagen, cellulose, TPE, Medtronic silicone, or SurgiWrap [70:30 poly(l-lactide-co-D, L-lactide); see fig. S1]. Printing parameters were as follows: nozzle size, 27 gauge; writing speed, 10 mm s⁻¹; pressure, 150 kPa; infill, 100% perimeter, 0.01 mm. The design and geometry of the printed graphene electrodes are shown in fig. S1. A thin layer (~500 μm) of Voltaglue bioadhesive (~30 mg) was spread over the electrode patch using a laboratory microspatula, and the resulting assembly is referred to as ePATCH throughout the text (see fig. S1).

**Minimally invasive catheter with retractable electrodes**

A polyurethane balloon for an ultrasonic endoscope (Olympus, MAJ-1351) was bonded over the main shaft (12 Fr, 4-mm diameter, and 22-cm length; Cook Medical) of the catheter using a Locite 422 adhesive. For the anode and the cathode shafts, a wedge pressure catheter (4 Fr, 1.3 mm in diameter; Teleflex Medical Ltd.) was trimmed from both proximal and distal sides so that 20 cm of the middle lumen remained. Two of these lumens were bonded on two diametrically opposite sides of the main shaft using a Locite 422 adhesive. Flexible stainless steel tubing (0.5 mm outer diameter, 0.13 mm wall thickness, and 0.25 mm inner diameter), purchased from McMaster-Carr, was housed in the cathode and anode shafts to transfer the voltage from the distal to the proximal end of the catheter. Shape memory nitinol wires (0.25 mm diameter; purchased from McMaster-Carr) were fixed on the distal sides of the stainless steel tubing. The nitinol wires and the nitinol wire/stainless steel joints were covered with Micro-Renathane tubing (polyurethane, 0.6 mm diameter; Braintree Scientific; see fig. S2). The cathode and the anode nitinol wires were threaded into the patch. The ePATCH was then coiled around the balloon using the deformation of the nitinol wires to assist with folding (fig. S3). The miniaturized catheter (fig. S4) was fabricated similarly, with the exception that the main shaft was created using a balloon wedge pressure catheter (6 Fr, 2-mm diameter; Teleflex Medical Ltd.) trimmed to a length of 22 cm.

**Real-time rheology**

Viscoelastic mechanical properties were measured with a parallel plate rheometer setup (TA-65 Instruments, AR 2000). The ePATCH was affixed on the bottom Peltier plate of the rheometer with double-sided tape. The Voltaglue was activated via CATRE by supplying a DC of 1 to 3 mA from a Keithley 2450 SourceMeter. All experiments were performed in real time at room temperature at 1% strain and 1-Hz oscillation with a 25-mm parallel plate probe (stainless steel), maintained at a gap of 0.30 mm.

**Electric current/field simulation through nearby tissues**

For electric field finite element simulations, a 3D model was built using the software COMSOL Multiphysics, V5.1, USA (fig. S5).
For simplicity, all the layers were modeled as homogenous, isotropic conductors with constant conductivity and relative permittivity throughout. Graphene electrodes were assigned a conductivity of 875 S m$^{-1}$ and a relative permittivity of 500. The biocompatible substrate was assigned a conductivity of $10^{-6}$ S m$^{-1}$ and a relative permittivity of 2. An electric current of 2 mA was established between the cathode and the anode. AC/DC module with the electric current interface was used to simulate the electric potential and electric field lines.

For electric current feedback, a stainless steel needle was inserted in the porcine heart tissue slice (20 mm by 20 mm by 2 mm) at a depth of 1 mm. Keithley 2450 SourceMeter was used as an ammeter to record stray electric current across the needle. Next, the ePATCH was placed on the top of the porcine heart tissue, and Voltaglue was electrocured using 2 mA with a different current source. Simultaneously, the electric current was recorded across the needle in real time by the ammeter.

**Morphology of tissue/bioadhesive interface**
The cross section of the tissue/bioadhesive interface was imaged by a scanning electron microscope (SEM). Electrocured bioadhesive samples on tissue substrates were freeze-dried for 12 hours, and imaging was performed using Zeiss Merlin high-resolution SEM at an acceleration voltage of 1 kV and a working distance of 5 to 6 mm.

**Adhesion characterization of ePATCH against biological tissues**

**Lap shear**
The maximum lap shear at failure was measured according to a modified ASTM F2255-05 protocol. Biological tissue (porcine heart or aorta) sections of 2 cm by 2 cm and ePATCH were bonded on microscopic glass slides using Loctite 422 and double-sided tape (McMaster-Carr), respectively. Voltaglue was cured for 5 min via CATRE with a DC of 1 to 3 mA from a Keithley 2450 SourceMeter. DuraSeal was used as a control. DuraSeal is a commercially available sealant that consists of two components, in which polyethylene glycol–activated ester cross-links with trisylsine upon mixing, that is technically improbable within catheters. For DuraSeal ( Covidien) testing, a 300-μm-thick layer of sealant was sandwiched between the biocompatible patch and biological tissue sections and cured for 5 min. Lap shear strength was quantified using a mechanical tensile tester with a 2-kN force cell (Instron 5944), and a linear extension of 3 mm min$^{-1}$. The accuracy of the force measurement with the 2-kN load cell is ±0.5% of the reading. The fresh biological tissues including the porcine heart and porcine aorta were purchased from Sierra For Medical Science Inc., California. Porcine carotid and renal arteries were purchased from Sierra For Medical Science Inc., California. A defect of 2 mm was created in the renal artery before anastomosing it and bonding it with the carotid artery.

**Fistula models**
The ex vivo biological fistula model was created in the laboratory by adjoining a porcine renal and a carotid artery using a flexible adhesive (Sil-Poxy, Smooth-On). Porcine carotid and renal arteries were purchased from Sierra For Medical Science Inc., California. A defect of 2 mm was created in the larger diameter graft before its bonding with the smaller graft. The entire fistula model was coated with a soft silicone elastomer (Ecoflex 00-20, Smooth-On) for sealing purposes, in the absence of blood clotting factors. The vascular fistula defects were closed by the electroceutical catheter with a DC of 3 mA from a Keithley 2450 SourceMeter and subsequently evaluated for tissue sealing.

**Closure of ex vivo carotid artery defects**
A 2-mm defect was created in fresh porcine carotid arteries (Sierra For Medical Science Inc., California). Porcine defects were sealed with the electroceutical catheter with a DC of 3 mA from a Keithley 2450 SourceMeter. MT staining was performed to evaluate the interaction of ePATCH with biological tissues at the interface. The carotid arteries were fixed with 10% formalin (Carolina Biological Supply). Closure of carotid artery defects in presence of heparin-infused blood was illustrated with H&E-stained cross sections of ~10 μm in thickness.

**Demonstration of defect sealing under continuous/pulsatile flow**
Ex vivo swine aorta with a 3-mm defect was connected to a mock circulatory loop. Sodium citrate–infused porcine blood (purchased from Sierra For Medical Science Inc., California) was circulated at a rate of 10 ml min$^{-1}$ through the assembly using a syringe pump. ePATCH was electrocured for 5 min via CATRE with a DC of 3 mA from a Keithley 2450 SourceMeter.
The ability of the patch to withstand the pulsatile flow like physiological conditions was evaluated against collagen tubes (Nippi, Japan) with a diameter of 3 cm. A synthetic blood fluid (1,2-ethanediol (monooethylene glycol) with 20% glycerine additive; diluted by 25% with water) that mimics blood viscosity (~3 cP) was circulated under pulsatile flow (60 to 125 mmHg; Harvard Apparatus, USA) at a mean flow rate of 2 liters min⁻¹. Three defects, each 2 mm in diameter, were created and subsequently sealed via the electroceutical catheter with a DC of 3 mA from a Keithley 2450 SourceMeter.

**Evaluation of the thrombogenic potential**
Square patches (1 cm by 1 cm) of a biocompatible substrate, graphene electrodes, DuraSeal, uncured, electrocured, and UV-cured Voltaglue were incubated with heparin-stabilized porcine blood (Sierra For Medical Science Inc., California; following the protocol in reference) for 1 hour at 37°C on a hematology mixer, as per the published protocol (60). The uncured, electrocured, and UV-cured Voltaglue samples were washed with heparin [5% (w/v) in 1x PBS] before incubation, as published previously (33). Heparin wash was used to remove the electrostatic interactions. The surfaces were rinsed three times with 50 mL of PBS after incubation in blood and then immersed in 1 mL of 2% Triton X-100 solution for 20 min to lyse surface adherent platelets. The number of deposited platelets on each specimen was then quantified by a LDH assay with the LDH-Glo Cytotoxicity Assay Kit (Promega). The Lumino metric readings were recorded using VarioskanFlash 4.00.53 (Thermo Fisher Scientific Inc.) and SkanIt software 2.4.5 RE for Varioskan Flash.

**In vivo ePATCH activation**
In vivo electrocuring was performed on a rat's heart in Sprague-Dawley female rats. Electrode patches were soaked in 70% ethanol for 30 min before the procedure. All procedures were performed in accordance with Massachusetts Institute of Technology’s Committee on Animal Care (protocol number 0118-006-21). Sprague-Dawley female rats (300 to 350 g) were anesthetized with isoflurane 2 to 3%, tracheal intubation was performed, and animals were connected to a mechanical ventilator (Model 683, Harvard Apparatus) and placed over a heating pad for the duration of the surgery. A thoracotomy was performed between the third or fourth left intercostal space. The heart was exposed, and the ePATCH was delivered to the heart. In vivo electrocuring was performed on the epicardium of the heart via the modified miniaturized catheter, supplying a DC of 3 mA for 5 min. Real-time ECG was recorded during the electrocuring via a lead II configuration using the PowerLab from ADInstruments data acquisition. Following the procedure, the hearts were excised and fixed in 10% formalin for 24 hours for H&E histological analysis.

**Statistical analysis**
All data are presented as means ± SD (n = 3, unless stated otherwise). The significance was evaluated with OriginPro 2019 64-bit software by a one-way analysis of variance (ANOVA) with Tukey correction as a post hoc test. *P < 0.05 was considered to be statistically significant. Ex vivo proof-of-concept testing involved sample sizes from one to five. The sample size for in vivo electrocuring in small animals was two.

**SUPPLEMENTARY MATERIALS**
Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/7/14/eabf6855/DC1

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