Bioinspired liquid gating membrane-based catheter with anticoagulation and positionally drug release properties

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Catheters are indispensable medical devices that are extensively used in daily medical treatment. However, existing catheter materials continue to encounter many problems, such as thrombosis, single functionality, and inadaptability to environmental changes. Inspired by blood vessels, we develop a self-adaptive liquid gating membrane-based catheter with anticoagulation and positionally drug release properties. Our multifunctional liquid gating membrane-based catheter significantly attenuates blood clot formation and can be used as a general catheter design strategy to offer various drugs positionally releasing applications to comprehensively enhance the safety, functionality, and performance of medical catheters’ materials.

INTRODUCTION

Catheters are thin flexible tubes that can be inserted into the body, creating channels for the passage of fluids or the entry of surgical devices (1–4). When placed within the lumen of veins, the presence of catheters decreases blood flow, and blood can thus begin to coagulate, turning free-flowing liquid to blood clots or films, which potentially cause thrombotic complications (5). In addition, it is presumed that the size of the catheter can have a great impact on the incidence of thrombosis; thus, the catheter-to-vein ratio requires extra attention in selecting appropriate-sized devices for vessels (6). However, as therapeutic doses can all produce a degree of anticoagulation that is considered a major risk (7), the development of catheter materials with anticoagulation property and size adaptivity is imperative. Various strategies focusing on material fabrications to reduce blood coagulation while improving the biocompatibility of catheters include chemical modifications (8–10) and construction of micro- and nanostructures (11, 12). Although anticoagulation performance is realized, such approaches can also lead to increased sophistication in material processing and will be impeded by technical processing bottlenecks, especially when handling miniaturization demand.

Recently, the use of liquid to infuse structured surfaces in biomedical applications shows exceptional antibiofouling performance (13–17). For example, liquid-infused materials have shown potential in preventing catheter-associated urinary tract infections (18), where the developed liquid-infused surfaces in catheters exhibit a desirable combination by incorporating antifouling advantages with the active release of bactericidal agents. Moreover, with a trend toward increasing the use of catheters for wider indications (19–21), adaptive applications to environmental changes and flexible and controllable drug release can greatly enhance catheters’ safety and functionality.

A new liquid gating membrane material was put forward, where liquids can be used as structural materials with gating functions and new applications to be controllably and stably confined in space by capillary forces (22, 23). Rather than reconfiguring the solid geometry (24) or relying on molecular switches (25) or external gates (26), the membrane takes advantage of the unique ability of a fluid to deform and reconfigure in situ to respond to capillary pressure. Thus, it would bring many new potential applications, which could not be realized in traditional membrane materials (27–31).

Inspired by blood vessels with adaptive tube size changes (32) and specific mass transfer pathways on the vascular wall (33), here we further extend the function of liquid gating membranes by using the membrane material that intrinsically has differential response profiles for a broad spectrum of fluids over a wide range of environmental pressures with virtually no fouling for complex fluids. Compared with previous materials (34, 35), this bioinspired liquid gating membrane-based catheter (LGMC) has the advantage of tube size adaptivity and having anticoagulation and positionally drug release properties. Such a material, as an example, could potentially spark further experimental and theoretical efforts with the choice of different functional matrices (36, 37) and gating liquids for the exploitation of more complex catheter applications.

RESULTS

Design and preparation of LGMC

As shown in Fig. 1, we prepared a microporous membrane-based catheter using the well-developed electrospinning method. The effective pore size, used as one of the key factors to determine the catheter working pressure range of a polyvinilidene fluoride (PVDF) porous membrane, is selected and controlled by different electrospinning parameters (figs. S1 and S2 and see the Supplementary Materials). The transport pressure of fluids inside the catheter must be lower than the transmembrane pressure threshold of the liquid gating membrane to ensure the safe transport of the fluids without leaking out of the catheter wall. The pressure threshold of the liquid

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gating membrane is determined by the effective pore sizes of the porous membrane and the affinity of the gating liquid to the porous membrane. Therefore, gating liquid selection is also a key factor for the new catheter materials. The gating liquid is selected on the basis of two points: (i) it should have a good affinity with the membrane to obtain stability and (ii) it should have specific functions for medical applications (Fig. 1A). In our case, we selected perfluorodecalin, Krytox 100, Krytox 103, and silicone oil 500 because of their strong affinity with PVDF and good biocompatibility (13, 38–40).

Blood circulates through blood vessels, and the tunable vessel size is considerably important, as it helps to maintain the pressure of blood moving through the vascular system. Different from their tough external layer, the inner surface of blood vessels is lined with endothelium, providing a continuous layer to regulate substance exchange between blood and tissues, to regulate clots, and to detect and respond to changes in blood pressure and flows (32). Inspired by blood vessels, our approach uses a continuous fluid layer to endow catheters with properties including tube size adaptivity, anticoagulation, and mass transfer regulation on the catheter wall to realize positionally drug release (Fig. 1B).

**Controllability and stability experiments**

Catheters with different diameters can be directly prepared by the electrospinning method (Fig. 2A), but the effective pore size of the catheter membrane needs to be optimized to obtain the required gating threshold of the transmembrane pressure. The pressure thresholds of the liquid gating membranes were evaluated by a customized transmembrane pressure measurement (fig. S3 and see the Supplementary Materials). Details of the microporous membrane preparation with different pore sizes are given in Materials and Methods. There are two key parameters for the preparation of porous membrane materials: the concentration of the electrospinning solution and the electrospinning working voltage. Electrospinning time duration, however, will not notably affect the effective pore sizes but can increase the membrane thickness, and the increased thickness of the membrane may result in higher pressure thresholds (Fig. S4 and see the Supplementary Materials). By increasing the electrospinning solution concentration, the pressure thresholds of the liquid gating membranes will decrease exponentially (Fig. 2B), but the lower the concentration, the lower the porosity of the membranes (Fig. 2C and fig. S1 and see the Supplementary Materials). In our case, to balance the pressure threshold and the porosity of the membrane, we select the concentration at the mass fraction of 15.9% with the thickness of the membrane at about 45 μm in the following experiments. The working voltage was also investigated to optimize the preparation of membrane materials (fig. S2 and see the Supplementary Materials). We used 10 and 25 kV to prepare the membrane at the same concentration solution. The higher the voltage, the less the fibrous structure in the obtained membrane will be, corresponding to the decrease of the effective pore size and reduction in the stability of the pressure threshold, due to the uneven distribution of the lamellar structure (fig. S2B and see the Supplementary Materials). Therefore, 10 kV is selected in the following experiments.

Next, the affinity of the gating liquid to the porous membrane material was studied. Theoretically, to establish a stable LGMC, the total interfacial energies per unit area (E) of the three configurations shown in Fig. 2D are required. Configuration 1 involves a gating liquid that is infiltrated into and has strong affinity with the porous membrane, with a transport fluid around (E₁); configuration 2 involves the transport fluid being infused into the porous membrane instead of the gating liquid (E₂); configuration 3 involves the gating liquid being infused into the porous membrane (E₃). To ensure that the gating liquid will not be replaced by the transport fluid,
one should meet and satisfy $\Delta E_1 = E_2 - E_1 > 0$ and $\Delta E_\text{II} = E_2 - E_3 > 0$. According to the physicochemical properties of these configurations

$$\Delta E_1 = R \cdot (\gamma_B \cdot \cos \theta_B - \gamma_A \cdot \cos \theta_A) - \gamma_{AB}$$  

(1)

$$\Delta E_\text{II} = R \cdot (\gamma_B \cdot \cos \theta_B - \gamma_A \cdot \cos \theta_A) - \gamma_B$$  

(2)

where $\gamma_A$ and $\gamma_B$ are the surface tensions of transport fluid and gating liquid, respectively; $\gamma_{AB}$ is the interfacial tension between transport fluid and gating liquid; and $\theta_A$ and $\theta_B$ are the contact angles of transport fluid and gating liquid on the porous membranes, respectively. $R$ is the roughness factor of the porous membranes (the ratio between the apparent and projected surface areas) (see the Supplementary Materials for more details) (15). If both $\Delta E_1$ and $\Delta E_\text{II}$ are positive, the LGMC is stable in theory; if neither $\Delta E_1$ nor $\Delta E_\text{II}$ is positive, the catheter is unstable in theory. In addition, the biocompatible property of the gating liquid needs to be taken into account. Therefore, perfluorodecalin, silicone oil 500, Krytox 100, and Krytox 103 are selected and tested. The results are shown in Table 1, and according to the specific experimental requirements, we can select the optimum gating liquid.

Blood flows in the vessels, in which persistent shear stresses are applied on the vessel walls. As for the LGMC, shear stability is also studied. Cone-plate shear testing is used to characterize the shear stability of LGMCs (Fig. 2E). It indicates that by selecting Krytox 100, less than 5° of sliding angle exists at a shear rate of 500 s$^{-1}$, and less than 10° exists at all shear rates from 1000 to 2500 s$^{-1}$. The shear stability can be further improved through tailoring of the gating liquids. Meanwhile, driven by the capillary pressure, a portion of the gating liquid infiltrates the pores in the porous membrane, while others distribute on the surface of the membrane (fig. S5 and see the Supplementary Materials). When the applied pressure of transport fluids overcomes the capillary pressure but below the pressure threshold, the gating liquid will be dynamically distributed inside the membrane and both sides of the catheter wall. Our hypothesis is that this behavior can be used to achieve the self-adaptive tube size.
control of the catheter. To verify it, fluorescein is added into the gating liquid, and a confocal laser scanning microscope is used to confirm this result by detecting the dynamical change of the gating liquid at the upper parallel wall surface with changing the applied pressure of transport fluids (Fig. 2F). In addition, owing to the inherent dynamic property of the gating liquid, LGMC is supposed to naturally restore itself when facing physical damage through molecular turnover and local flow (fig. S6 and see the Supplementary Materials).

### Biocompatibility and anticoagulation tests

Biocompatibility is a prerequisite for medical catheters. Thus, blood compatibility, including hemolysis ratio, clotting parameters, and cytocompatibility [via Cell Counting Kit-8 (CCK-8) test and cytoskeleton staining test], were determined to characterize the biocompatibility of the LGMC (Fig. 3). Figure 3A shows that a bare PVDF catheter has a higher hemolysis ratio than LGMC, and Fig. 3B shows no statistical significance in the tests of fibrinogen content (FIB), activated partial thromboplastin time (APTT), and thrombin time (TT) between the bare PVDF and the LGMC. Prothrombin time (PT) for LGMC, however, is significantly longer than that of the bare PVDF. Longer PT represents slower coagulation. Therefore, compared with the only solid-state membrane-based catheter, LGMC has better blood compatibility. Meanwhile, CCK-8 is a sensitive colorimetric assay used to detect cell proliferation and toxicity. Higher optical density (OD) values represent better cytocompatibility. As shown in Fig. 3C, it indicates that LGMC is not less cytocompatible

| Microporous membranes | Gating liquid | Transport fluid | $\gamma_A$ | $\gamma_B$ | $\gamma_{AB}$ | $\theta_A$ | $\theta_B$ | $\Delta E_I$ | $\Delta E_{II}$ | Stable? |
|-----------------------|---------------|----------------|---------|---------|-------------|---------|---------|-----------|-----------|-------|
| 9.2% PVDF             | Perfluorodecalin | DI water       | 72.4    | 17.8    | 53.9        | 95.2    | 0       | −5.3      | 30.8      | Y/N   |
| 11.4% PVDF            | Perfluorodecalin | DI water       | 72.4    | 17.8    | 53.9        | 126.2   | 0       | 67.2      | 103.4     | Y     |
| 13.7% PVDF            | Perfluorodecalin | DI water       | 72.4    | 17.8    | 53.9        | 133.3   | 0       | 81.0      | 117.2     | Y     |
| 15.9% PVDF            | Perfluorodecalin | DI water       | 72.4    | 17.8    | 53.9        | 127.9   | 0       | −70.72    | 106.9     | Y     |
| 18.1% PVDF            | Perfluorodecalin | DI water       | 72.4    | 17.8    | 53.9        | 72.4    | 0       | −62.1     | −26.0     | N/N   |
| 15.9% PVDF            | Krytox 100      | DI water       | 72.4    | 16.4    | 23.6        | 127.9   | 0       | 90.2      | 105.4     | Y     |
| 15.9% PVDF            | Krytox 103      | DI water       | 72.4    | 17.1    | 24.9        | 127.9   | 0       | 98.6      | 106.2     | Y     |
| 15.9% PVDF            | Silicone oil 500 | DI water       | 72.4    | 20.2    | 37.0        | 127.9   | 0       | 92.5      | 109.3     | Y     |

Fig. 3. Biocompatibility and anticoagulation property of the LGMC. (A) Hemolysis ratio, in which the value of LGMC is significantly lower than that of the bare PVDF catheter. (B) Normalized clotting parameters of the bare PVDF and LGMC based on black values. (C) Cytocompatibility of the bare PVDF and LGMC, in which the histogram shows the cytotoxicity result based on the CCK-8 kit, and confocal images reveal the morphology of cells attached on LGMC. (D) SEM images of platelet adhesion on the bare PVDF and LGMC. (E) Statistical analysis of platelet adhesion numbers on PVDF and LGMC based on three replicates. (F) Whole blood drops sliding off the LGMC with no trails behind while keeping still on the PVDF at the same tilt angle (30°) (scale bar, 5 mm). (G) Photographs of PVDF and LGMC after exposure to whole blood for 30 min, with a flow rate of 4 ml min$^{-1}$. Histogram values are a statistical analysis of red pixels using Photoshop in the same operation (*$P < 0.05$). (Photo credit: Chunyan Wang, Xiamen University.)
Positionally drug release performance

As mentioned above, many catheters are used for drug releases, and the releasing processes can only be achieved at the catheter port, which limits the flexibility and controllability of the drug release. LGMC has the gating liquid that is dynamically distributed through the porous membrane, which can be used as a specific mass transfer pathway on the catheter wall to positionally control drug release properties. To further demonstrate this, fluorescent molecules are also selected as simulated drugs to add into the gating liquid. Figure 4A shows the diagrams of LGMC used for the drug release experiments, and detection position is selected at the top longitudinal section of LGMC. Figure 4B shows the confocal images of the three detection positions during the drug release from the selected site of the LGMC, and the results prove that LGMC can be used in positioning control of drug release applications. In addition, considering that the drugs may be hydrophilic or hydrophobic molecules, both oil-soluble and water-soluble molecules are further tested to verify the universality of LGMC (Fig. 4C).

DISCUSSION

In summary, we introduce a bioinspired self-adaptive LGMC with anticoagulation and positionally drug release properties. Theoretical modeling and experiments demonstrate the adaptive tube size control of the catheter, which is achieved by the stable interfacial design of the affinity of the gating liquid to the porous membrane, and the gating liquid can dynamically distribute inside the porous membrane and both sides of the catheter wall. Meanwhile, the biocompatible gating liquid provides anticoagulation properties for the catheter application, and it can be extended to be the liquid-based specific mass transfer pathway on the catheter wall to be used further in positionally drug release applications.

In addition, although the proof of concept shows the viability of the goals with LGMCs, it is hoped to spark further researches in this field to accelerate their translation into practice. For instance, the mechanical properties of clinically used catheter materials are factors of importance during their manipulation into vascular branches with or without the aid of a steering equipment. As the LGMC is constructed on a microporous tube infiltrated with a designed gating liquid, many prospective technologies, such as three-dimensional (3D) printing, pore-forming agent–based fabrication, etc., can also be exploited with different materials for preparing matrices according to operational standards. In addition, the drug release properties that are desirable for real practice can attract research attention in terms of drug release kinetics for different molecules and point-to-point precise control in real applications, since drug release performances can vary with the molecules, the constituents that the LGMC system used, and the peripheral conditions where the catheter is placed. All in all, more targeted researches are expected for each specific real-life scenario. Although improvements are required, our new catheter material design is an example of the beginning of a multifunctional catheter and moves one step further to comprehensively enhance the safety, functionality, and performance of medical catheters for the development of "smart" catheter materials for real-world applications.

MATERIALS AND METHODS

Experimental design

PVDF polymers (Mn = 500,000) dissolved in 1:1 N,N-dimethylacetamide/acetone were used for electrospinning microporous catheters. Perfluorodecalin, silicone oil 500, Krytox 100, and Krytox 103 were used as gating liquids for specific experiments in this research. LGMCs were generated by infusing the exact gating liquid into the microporous membrane-based catheter, with a dropping amount of 10 μl cm⁻². To observe the positionally drug release behaviors, however, both water-soluble (rhodamine B) and oil-soluble (fluorescent yellow 131SC) fluorescents were used as drug indications.

Shape characterization

The overall appearances of the electrospinning microporous membrane-based catheters were taken by a digital camera (AF-S MICRO, Nikon).
A further amplified topography of the catheter with 1.5 mm diameter was observed by a digital microscope (SK2300U, Keyence).

Transmembrane pressure threshold measurement
Transmembrane pressure thresholds of the LGMCs were measured by a wet/wet current output differential pressure transmitter (PX273-100DI, Omega), with a flow of gas (2 ml min⁻¹). A Harvard Apparatus PHD ULTRA syringe pump with two syringes (50 ml) was used in all experiments.

SEM characterization
To characterize the surface morphologies of the microporous membranes, a scanning electron microscope (SEM) (Hitachi s-4800, Japan) was used. Before SEM observation, platinum was sputter-coated on the membranes.

Stability characterization
Energy criteria–related water contact angles, surface/interfacial tensions, and shear stability–related sliding angles were all measured by the OCA100 system (DataPhysics, Germany). For water contact angles, small droplets of deionized (DI) water (3 μl) were dropped on different microporous membranes, and images were taken until they balanced. Water contact angles were then derived. Surface/interfacial tensions were measured through a pendant drop method. Droplet volumes for them were as large as possible and varied with the liquids and the media. Moreover, for interfacial tensions, lighter liquids were dripped into heavier media. Sliding angle was defined as the angle at which a droplet of liquid begins to move across a surface. The TBU method was used to test sliding angles, with a tilting speed at 0.1° min⁻¹. A 3-μl water droplet was dropped on the pretreated LGMC, and the pretreating processes were as below: LGMC was exposed to shear using a rheometer (MCR 302) with a 40-mm-diameter, 2° cone-plate setup. The cone plate was lowered down to 103 μm above the LGMC. Different shear rates were progressively conducted. Time duration for each sample was 10 min. Glycerol (35%, v/v) in water was used as a medium.

Dynamic performance
The dynamic property of LGMC was characterized by a confocal laser scanning microscope (TCS SPS, Leica). A semicircular LGMC sticking to a glass slide was prepared at the beginning. The gating liquid (silicone oil 500) was doped with fluorescent yellow 131SC to make it visible. 3D reconstruction was carried out to construct the semicircular LGMC used. A Harvard Apparatus PHD ULTRA Syringe Pump was used to control the inner pressure, and images focusing on the top longitudinal section of LGMC were taken (xyz mode) with the pressure changes.

Biocompatibility characterization
Hemolysis ratio test, clotting parameter test, CCK-8 test, cytoskeleton staining test, and platelet adhesion test were carried out following the typical processes or the manual protocols. More details can be found in the Supplementary Materials.

Anticoagulation tests
Repellence of whole blood and suppression of coagulation under flow tests were carried out to show the anticoagulation performance. For the repellence of whole blood, a 30° tilt support was built, and microporous PVDF membranes and LGMCs were stuck to the lumen of a semicircular tube with a diameter of 1.6 cm. Rabbit whole blood (50 μl) with 0.109 M sodium citrate was then dropped on the top of the semicircular tube. Movies were taken by a digital camera, and screenshots at specific points were shown. Suppression of coagulation under the flow in vitro experiment was carried out with a peristaltic pump. The flow rate of rabbit whole blood was 4 ml min⁻¹, and the time duration was half an hour. After flowing, photos were taken and analyzed by Photoshop with the same operation.

Drug release performance
The semicircular LGMC sticking to a glass slide was also used for drug release experiments, with fluorescent dyes as indicators. While the semicircular LGMC was in place, the fluorescent solution (1 μl) was dropped on it, and at the same time, confocal images (xy mode) of the detection positions were taken. Both oil-soluble (fluorescent yellow 131SC) and water-soluble (rhodamine B) molecules were dissolved into the gating liquid silicone oil 500 to form the fluorescent solution. The transport fluid was DI water.

Statistical analysis
One-way analysis of variance (ANOVA) was used to calculate the statistically significant difference (P), followed by a Tukey’s multiple comparison test. SPSS software was applied to conduct statistical analysis, and P < 0.05 was considered to be statistically significant. For all experiments, at least three parallel groups were tested.

Biological ethics
There are no ethical conflicts involved in this work. All animal-related procedures were performed in accordance with the protocol #120774 approved by the Institutional Animal Care and Use Committee of Xiamen University. A male New Zealand rabbit (10 weeks old) was purchased from Slark Laboratory Animals LLC (Shanghai, China). Whole human blood was obtained from healthy volunteers with informed consent.

SUPPLEMENTARY MATERIALS
Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/6/36/eabb4700/DC1

View/request a protocol for this paper from Bio-protocol.

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