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Original Article

Novel device prototyping for endoscopic cell sheet transplantation using a three-dimensional printed simulator

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ABSTRACT

Introduction: Considering higher risks of candidates for cardiac regenerative therapy with compromised cardiac function, it is anticipated to develop less invasive surgical procedures. In the present study, we aimed to develop a prototype of totally endoscopic cell sheet delivery device and evaluate the surgical technique for epicardial cell sheet placement using three-dimensional (3D) printed simulators based on human computed tomography data.

Methods: We designed an endoscopic cell sheet delivery device with outer and inner frame with self-expandable applicator which can be opened in thoracic cavity. We launched spout line to provide liquids on the applicator surface and tension line to gently bend the applicator dorsally. We prepared human mesenchymal stem cell (MSC) sheets and compared wet/dry conditions of 3D printed heart/porcine heart and applicator to identify suitable conditions for cell sheet transplantation. Finally we validated the feasibility of endoscopic transplantation to anterior and lateral wall of left ventricle using 3D printed simulators.

Results: Moist condition of both 3D printed heart/porcine heart surface and applicator at transplantation yielded highest successful rate (100%, $p = 0.0197$). For both endoscopic transplantation sites, MSC sheets were successfully deployed. The procedure duration was 157 ± 23 s for anterior wall and 123 ± 13 s for the lateral wall in average, respectively.

Conclusions: We developed a novel prototype of endoscopic cell sheet delivery device for minimally-invasive cardiac regenerative therapy utilizing a 3D printed simulator. The commercialization of the prototype may provide a safe minimally-invasive method to deliver potential cardiac regenerative therapy in the future.

1. Introduction

Stem cell products manufactured from various stem cell populations (e.g. bone marrow-derived hematopoietic stem or stromal cells, skeletal myoblasts, pluripotent stem cells) are being increasingly attempted to be applied for clinical use worldwide [1–5]. To deliver these stem cell products for heart diseases, trans-coronary injection, epicardial injection and cell sheet technique have been introduced [6]. Among them, cell sheet products are considered to hold higher efficiency of grafted cell survival compared to that in direct injection of cell suspension to the heart by virtue of preserved extracellular matrix proteins [7]. Previously, we have reported therapeutic potential of cardiac tissue sheets generated

Abbreviations: 3D, three dimensional; MSC, mesenchymal stem cell; TERT, telomerase reverse transcriptase; αMEM, alpha minimum essential medium; FBS, fetal bovine serum; EDTA, ethylenediaminetetraacetic acid; ECSheeD, endoscopic cell sheet delivery device; CT, computed tomography; LV, left ventricle.

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from differentiated cardiovascular lineage cells from mouse embryonic stem cells [8,9] or human induced pluripotent stem cells [10,11] for animal heart disease models as pre-clinical studies.

For the transplantation of cell sheet products, median sternotomy or lateral thoracotomy would be required to approach broad region of heart surface. In general, mediastinitis after open heart surgery occurs in 1.5–2% of patients [12–14], and the incidence is reported to be higher in heart transplantation patients under administration of immunosuppressants [15]. On the other hand, minimally invasive cardiac surgery with small skin incisions and limited surgical exposure is reported to associate with less surgical site infection [16]. Considering possible unavoidability of immunosuppressants due to allogeneic stem cell transplantation, providing minimally-invasive surgical procedures is mandatory to reduce the possibility of infections after surgery to standardize stem cell sheet transplantation therapies. In addition, minimally-invasive surgical procedure without full sternotomy, would reduce risks for future surgical interventions such as heart transplantation by avoiding tissue adhesion [17,18]. In the present study, we developed a novel endoscopic cell sheet delivery device for minimally-invasive surgical procedure, and validated the feasibility of the procedures of epicardial cell sheet delivery using three-dimensional (3D) printed simulators.

2. Methods

2.1. Three dimensional printed simulator

For the creation of 3D printed simulator, Inkjet 3D printer (IJOM, MFG No.0001, SCREEN Holdings, Co., Ltd., Kyoto, Japan) and vacuum casting machine (SANCRON SC-02, sid Co., Ltd., Saitama, Japan) were used. The creation of 3D printed simulators was conducted by crossMedical, Inc. (Kyoto, Japan) following designs made by authors.

2.2. Equipment for simulation experiments of cell sheet transplantation using thoracic cavity model

Equipment for procedures are shown in Supplemental Fig. 1. Three endoscopic ports were prepared: camera port [12 mm ENDOPATH xcel (Ethicon, Cincinnati, OH, USA)], forceps port [5.5 mm ENDOPATH xcel (Ethicon)] and ECSheeD port (for endoscopic cell sheet delivery device; small skin incision). The movies during procedures were recorded by 1488 HD Camera System (Stryker Japan K.K., Tokyo, Japan) and edited using Corel VdeoStudio ProX7 (Corel Japan Ltd., Tokyo, Japan).

2.3. Preparation of cells and cell sheets

Because of its proliferative capacity, we used immortalized human mesenchymal stem cell by transduction of telomerase reverse transcriptase (TERT) gene (TERT-hMSC) to generate cell sheets mimicking cardiac tissue sheets which we would like to apply for clinical use in the future. Briefly, to make bone marrow stroma-derived mesenchymal stem cell line immortal, TERT and human papilloma virus E6/E7 were transduced by retrovirus-mediated gene transfer. The presence and activity of the gene were confirmed by reverse transcription polymerase chain reaction. This TERT-hMSC were generously gifted from Toguchida Lab., Center for iPS cell Research and Application (CiRA), Kyoto University [19]. The experiments were approved by the Committee of Kyoto University as Recombinant DNA Experiments (#190366).

The cells were cultured in alpha minimum essential medium (αMEM) supplemented with 10% fetal bovine serum (FBS), 5.5 mmol/L 2-mercaptoethanol and 0.5 ml penicillin on non-coated 10-cm dish, at 37 °C in a humidified atmosphere of 5% CO_2/95% air. For the maintenance of TERT-hMSCs, the culture media were refreshed every 2 days. TERT-hMSCs were detached and dissociated into single cells by 3 min of incubation with 0.25% trypsin/ethylenediaminetetraacetic acid (EDTA) solution. We generated cell sheets by using temperature-responsive culture surface, UpCell® (CellSeed, Inc., Tokyo, Japan) following previously described methods [8–11]. At day 0, 5–6 million cells of TERT-hMSCs were seeded on FBS-coated 10-cm UpCell® with αMEM+10% FBS, and incubated at 37 °C in a humidified atmosphere of 5% CO_2/95% air. At day 4, MSC sheets were collected by spontaneous detachment from the UpCell® in room temperature. Then we collected the cell sheets from UpCell® and transferred them to non-coated 10-cm culture dishes filled with medium by pipets.

2.4. Statistical analysis

Categorical variables are reported as percentage of incidence in each experiments. Continuous variables are reported as means ± SEM. Data analyses were performed using JMP® Pro 14 (SAS Institute Inc., Cary, NC, USA). In comparisons of categorical data, p values were obtained with Fisher's exact test or Chi square test. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Prototyping of endoscopic cell sheet delivery device; ECSheeD

First, we designed and generated prototypes of the endoscopic cell sheet delivery device. Basic design of our Endoscopic Cell Sheet delivery Device (ECSheeD) is the combination of 1) outer stainless steel frame which can be inserted into the thoracic cavity through ECSheeD port, and 2) inner stainless steel frame with self-expandable applicator of cell sheets which can be installed in the outer frame while introduction into thoracic cavity and can be opened in the thoracic cavity after introduction (Fig. 1a). We used polyester-elastomer for the applicator because of its self-expandable capacity and the physical property with intermediate rigidity not to damage thoracic organs during cell sheet transplantation. During preliminary trials and errors, we found 2 conditions which should be controlled during transplantation procedures: 1) moist condition of applicator and heart surface, 2) gentle detachment of applicator after transplantation (not to make cell sheets detached from heart surface or distorted), and added 2 machineries for the prototype. To control moist conditions, we launched a spout line which can be connected to syringe to provide liquid on the applicator surface (Fig. 1a, c). To control the detachment of applicator, we launched a tension line which can be controlled to bend the applicator dorsally by turning the screw at another end of the device (outside of the body) (Fig. 1b). Final prototype was approximately 35 cm long, consisted of 18 mm diameter outer stainless steel frame and 10 mm diameter inner stainless steel frame with 5 × 3 cm polyester-elastomer as applicator at the top. Spout line and tension line were launched as well (Fig. 1c).

3.2. Three dimensional printed simulators

Next, we prepared 3D printed simulators to use for simulation experiments of transplantation surgery. The model consisted of several parts including heart, pericardium, lung, bone, muscle and skin. The model was designed by spatial information of adult male chest structures from computed tomography (CT) (Fig. 2). The heart model was made from ultra-soft material which is called “Ultra-Soft Precision Wet Model” by Ultraviolet-equipped inkjet printer

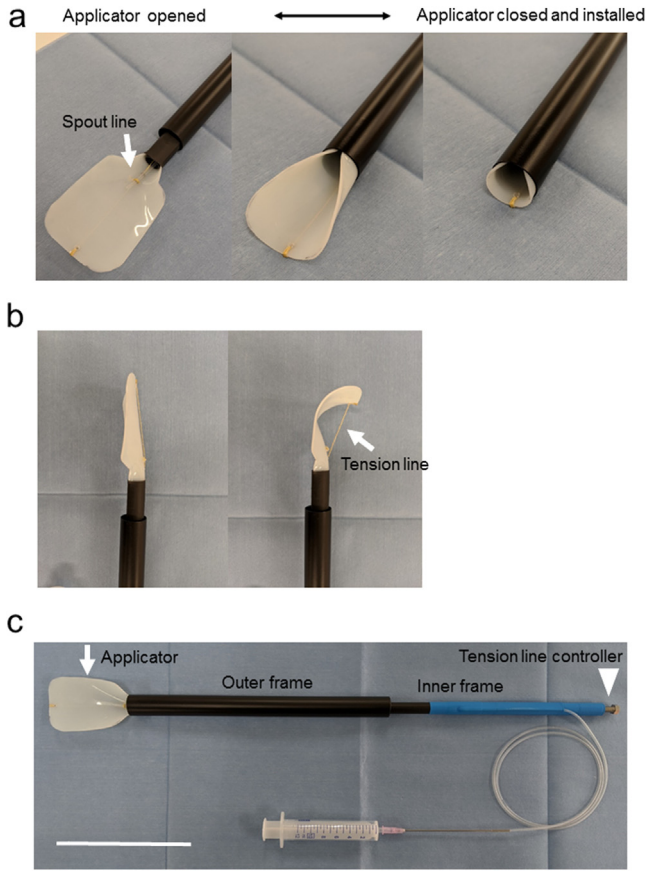

Fig. 1. Design of Endoscopic Cell Sheet delivery Device (ECSheeD). a: Top view of applicator. When the operator pulls inner frame, applicator can be installed in outer frame. Spout line is located at the center of the applicator (arrow). b: Side view of applicator. The applicator can be bended dorsally by turning the screw controller connected to tension line (arrow). c: Top view of ECSheeD. Applicator (arrow) and screw controller connected with tension line (arrowhead) are indicated. Scale bar: 10 cm.

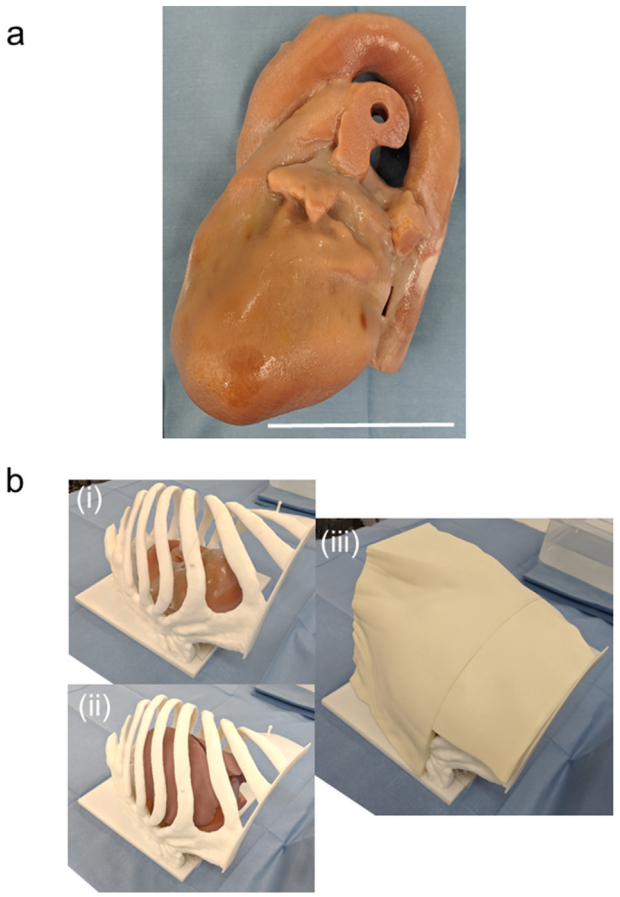

Fig. 2. 3D printed simulators. a: 3D printed heart model. Scale bar: 10cm. b: Thoracic cavity model. (i) heart (covered with transparent pericardium) and bone, (ii) lung (covering the heart) and bone, (iii) most outer structure of thorax.

technology (Fig. 2a), and thoracic cavity model (pericardium, lung, bone, muscle, skin) was made from polyurethane resin using vacuum casting method (Fig. 2b).

3.3. Optimization for transplantation procedures and conditions using 3D printed heart

Next, we attempted to optimize conditions of 3D printed heart and applicator for stable cell sheet transfer. We used properly trimmed nylon mesh (open 35 μm) to transfer the MSC sheets from culture dish to the applicator and set the nylon mesh with MSC sheets not to make MSC sheets directly touching to the applicator (Fig. 3a and b). To adequately leave a MSC sheet on the heart surface, we needed 2 steps: 1) leaving nylon mesh with MSC sheets from the applicator on the heart surface, 2) detaching nylon mesh from the heart surface with MSC sheets keeping attached to the heart surface.

As the 1st step, we attempted to identify conditions to adequately leave nylon mesh with MSC sheets on the heart surface. We set conditions as follows: #1 Dry/Dry, #2 Dry/Wet, #3 Wet/Dry, #4 Wet/Wet, respectively (heart/applicator). As shown in Table 1, most feasible condition for the detachment of nylon mesh from the applicator was “Wet/Wet” condition (100% in 20 times, $p = 0.0197$), indicating the importance of wet condition of both applicator and heart surface.

As the 2nd step, we tried to identify conditions for detaching nylon mesh from the heart surface with MSC sheet keeping attached to the heart surface. We set conditions as follows: #1 dry condition without sprinkling water, #2 wet condition with sprinkling water. As shown in Table 2, most feasible nylon mesh detachment condition was “wet condition with sprinkling water” before nylon mesh detachment (100% in 20 time attempts without tearing MSC sheets, $p = 0.0016$). Without sprinkling water, nylon mesh was tended to be detached with MSC sheet. So far, we confirmed that heart surface should be wet condition with sprinkling water, applicator surface should be wet condition with using water line before attachment of applicator on the 3D printed heart surface.

Additionally, we confirmed feasible surface condition using porcine heart based on the results as shown above (Fig. 3c). For the 1st step, the successful detachment ratio of nylon mesh from the applicator was 100% (10/10 times) when both applicator and porcine heart surface are wet. For the 2nd step, successful detachment ratio of nylon mesh with keeping MSC sheet on the porcine heart surface was 100% (10/10 times, average 1.6 [1–3] times of attempts) when sprinkling water before detachment of nylon mesh. These results indicate that the optimized conditions identified in 3D printed hearts work in cases of native heart as well.

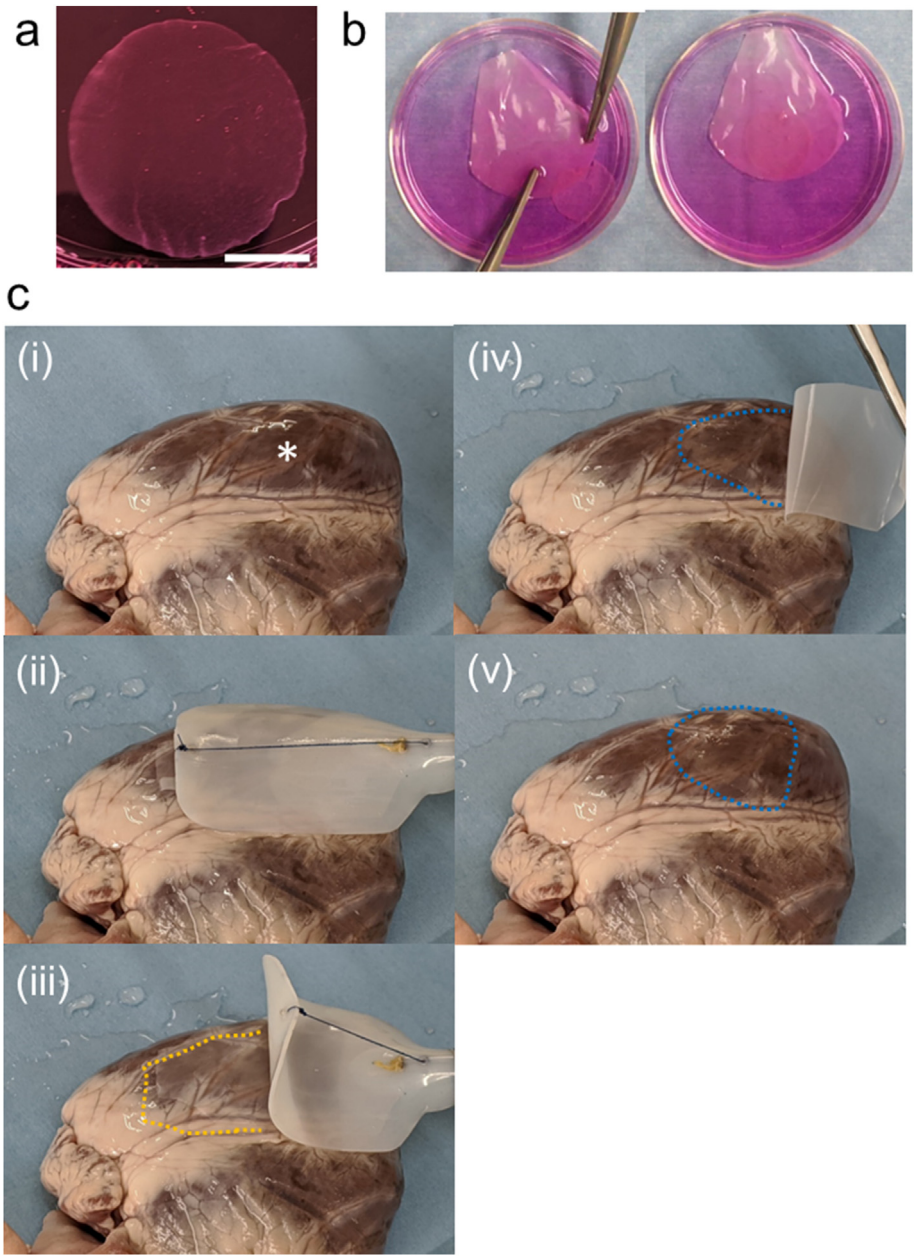

Fig. 3. Simulation experiments of MSC sheet transplantation for heart models. a: MSC sheet on the 10-cm UpCell dish. Scale bar: 1 cm. b: MSC sheet transfer using nylon mesh. c: MSC sheet transplantation on left ventricular anterior wall of porcine heart. (i) We sprinkled enough water to make porcine heart surface wet condition. Asterisk shows left ventricular anterior wall. (ii) The applicator with MSC sheet-loaded nylon mesh attached on the porcine heart surface. We moistened the applicator and nylon mesh through spout line. (iii) The applicator bended by tension line keeping nylon mesh attached (yellow dotted line). (iv), (v) After sprinkling enough water, we detached nylon mesh gently from the porcine heart surface to keep the MSC sheet on the heart surface (blue dotted line).

Table 1
Successful rate of mesh attachment according to moist conditions of 3D printed heart surface and applicator.

		Applicator surface	
		Dry	Wet
3D printed heart surface	Dry	75% (15/20)	70% (14/20)
	Wet	65% (13/20)	100% (20/20)*

*p = 0.0197.

Table 2
Successful rate of mesh detachment from MSC sheets according to moist conditions.

Mesh detachment	
With sprinkling water	Without sprinkling water
100% (20/20)**	60% (12/20)

**p = 0.0016.

Table 3
Experimental conditions for cell sheet application on each region.

Region	Position	Device insertion	Camera port (12 mm)	Forceps port (5.5 mm)
LV anterior wall	Right lateral 45°	5th mid clavicular line	3rd mid clavicular line	5th ant axillar line
LV lateral wall	Right lateral 90°	5th mid clavicular-ant. axillar line	4th ant. axillar line	5th mid axillar line

3.4. Three dimensional printed simulator study

Following the identification of feasible transfer condition of nylon mesh and MSC sheet, we tested MSC sheet transplantation procedures using ECSheeD and 3D printed simulator. After detachment of MSC sheets from culture dishes, we inserted trimmed nylon mesh between the sheet and culture dish and transferred the sheet-attached mesh to the applicator which covers the outlet of spout line. Applicator was installed into the outer frame (Video 1).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.reth.2020.10.007

For the 3D printed simulator experiments, three endoscopic ports were prepared: camera port, forceps port and ECSheeD port. We made small skin incision as the ECSheeD port because there was no commercially available port to fit the specific size of ECSheeD. The sites of ports were described in Table 3. After the pericardiotomy and pericardial retraction was made, ECSheeD was inserted into the thoracic cavity of the 3D printed simulator from ECSheeD port. Applicator was pushed out from the outer frame to be open in the thoracic cavity. Before landing the applicator on the heart, water was sprinkled to landing zone of the heart surface from forceps port (wet condition for heart surface). Water was pushed into the space between applicator and nylon mesh from the spout line after the landing of applicator (wet condition for applicator). After camera-based confirmation of the appropriate application of nylon mesh with cell sheet after gentle bending of the applicator (the 1st step), water was sprinkled again onto the nylon mesh, and the nylon mesh were removed by a forceps (the 2nd step) (Fig. 4a, Video 2). During the procedures, we held outer frame with one hand and additional procedures were done with another hand.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.reth.2020.10.007

We attempted endoscopic transplantation of MSC sheet to left ventricle (LV) anterior wall region and LV lateral wall region of the 3D printed heart and evaluated procedure duration (from insertion of ECSheeD into thoracic cavity to cell sheet transplantation), number of attempts and successful rate of nylon mesh detachment from applicator and cell sheet attachment at each site. As shown in Table 4, although several times of trials were required for

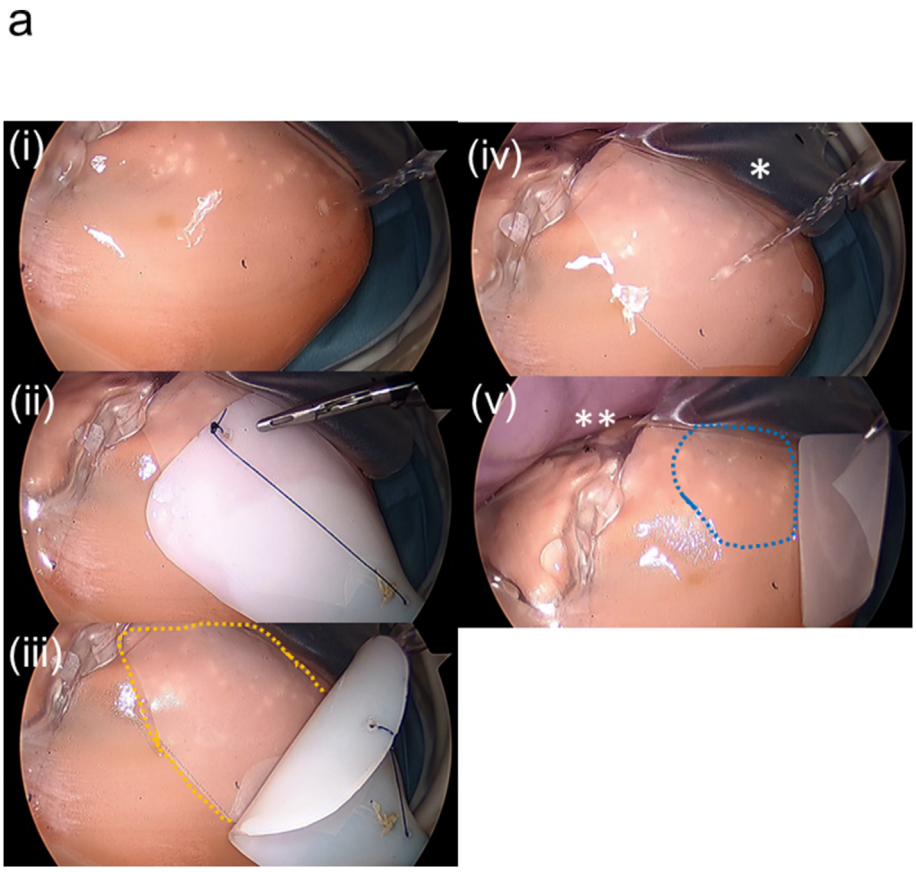

Fig. 4. Endoscopic transfer of MSC sheet using 3D printed thoracic cavity model. a: Images from endoscopic camera system during MSC sheet transplantation. (i) We sprinkled enough water through the forceps port to make 3D printed heart surface wet condition. (ii) After inserting main device, applicator was attached on the 3D printed heart surface. We moistened the applicator and nylon mesh through spout line. (iii) The applicator bended by tension line keeping nylon mesh attached on the 3D printed heart (yellow dotted line). (iv), (v) After sprinkling enough water through the forceps port, we detached nylon mesh gently from 3D printed heart surface by a endoscopic forceps. Transplanted MSC sheet is shown blue dotted line. Single asterisk (*) shows upwardly retracted pericardium. Double asterisk (**) shows compressed lung to lateral side.

Table 4
Attempts numbers and procedure durations of cell sheet transplantation using 3D printed simulator.

Region	Duration (sec)	Mesh detachment from applicator		Sheet attachment (successful mesh detachment)		
		# of attempts (mean)	successful rate	# of attempts (mean)	successful rate	
LV anterior wall	157 ± 23	1	100%	1.7 (1–3 times)	100%	N = 10
LV lateral wall	123 ± 13	1	100%	1.8 (1–3 times)	100%	N = 10

completion of sheet attachment (1.7 time attempts for LV anterior wall, 1.8 times attempts for LV lateral wall), all of mesh detachment from applicator were conducted in 1 time. Eventually, all MSC sheets were successfully deployed on the surface of 3D heart model without tearing, distortion, or dislocation of MSC sheets. The average procedure duration was 157 ± 23 s for LV anterior wall region and 123 ± 13 s for the LV lateral wall region, respectively.

4. Discussion

In the present study, we have developed a prototype of novel endoscopic epicardial cell sheet delivery device and validated the feasibility of transplantation procedures using 3D printed simulators highly recapitulating human thoracic structures which allowed us to perform repetitive simulation experiments to optimize the procedures of endoscopic cell sheet transplantation.

Cardiac regenerative medicine including stem cell sheet transplantation therapy would serve as an upcoming therapeutic modality in near future. Considering relatively higher risk of postoperative infection in candidates for regenerative medicine due to underlying impaired cardiac function and comorbidities [20,21], and potential immunocompromised status after allogeneic cell transplantation due to the administration of immunosuppressants, it is crucial to provide minimally-invasive therapeutic approaches without large skin incision and extensive surgical exposure. Previously, several cell sheet delivery and transplantation devices have been reported in various fields such as lung, esophagus, cornea and subcutaneous tissue [22–26]. In the present study, we have developed prototypes of a surgical device dedicated to endoscopic cell sheet transplantation targeting heart surface by launching several machineries such as spout line providing moist condition and tension line for gentle bending of the applicator which secured feasible quality in transplantation procedures. The commercialization of the device from the prototypes following further refinements may provide safer and standardized cell sheet therapy even for high-risk patients in the future.

Three-dimensional printed simulation models are increasingly applied in the field of cardiothoracic surgery. The 3D printed hearts based on human CT data would provide opportunities of pre-operative simulations and patient-specific pre-operative estimations for detailed anatomical deformity especially in valve and congenital heart diseases as well as trainings of intracardiac manipulations for surgeons [27–30]. The 3D model-based surgical trainings may hold advantages compared to those using animal hearts in reproduction of pathological changes of the heart which is especially valuable in rare anomalies, tolerance against repetitive use, easier preservation, and animal welfare. In the present study, we showed another application of the 3D printed simulator as a platform of the development of new surgical devices which may also allow us to reduce experimental animal usage and costs for the development of medical devices.

The present device for endoscopic cell sheet delivery may be applicable not only for the heart but for other organs with modifications considering the universal and rather simple design of the device. The application of the present device would not only be limited to cell sheet products but would be applicable for sheet-shaped products such as biodegradable biomaterial-based products as well (e.g. gelatin hydrogel sheets) [31]. The versatility of the present device in organ-wide and material-wide may broaden the possibility of the future clinical application of the device.

The 3D printed heart does not beat and may not completely recapitulate real *in vivo* surgical conditions of the cell sheet transplantation which would be the most critical limitation of the present study. To further validate the feasibility of operative procedures and stability of the cell sheets after transplantation optimized in the present study, we should investigate surgical implementation of the device for beating hearts including developing pressure during the transplantation procedure as well as functional evaluations of the hearts and histological evaluations for the engraftment of the cell sheets after transplantation using large animal models. Another option is to develop a modified 3D printed heart with beating machinery by the application of small pump inside which would more closely recapitulate human anatomical structures rather than those in animals. Further development of the device through the heart-beating models accessible to whole region of the heart would be anticipated towards clinical implementation of the device.

Although we confirmed fair attachment of the cell sheet on the heart model surface, it was difficult for us to distinguish which side is attached on the nylon mesh because the orientation became unclear during the transferring step. We would need to establish a method to distinguish the orientation if the cell sheet attachment is not sufficient in future experiments using beating heart models considering the preservation of adhesion molecules on the side adhered to the temperature-responsive culture dish bottom.

5. Conclusions

In the present study, we have developed a novel prototype of endoscopic epicardial cell sheet delivery device and confirmed the feasibility using a 3D printed simulator. Although further investigations are warranted, the results provided us the first step of successful and standardized cell sheet transplantation therapies through minimally-invasive approach which might have significant translational potential in regenerative medicine.

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Declaration of competing interest

H.O., H.M. and H.Y. are inventors of device-related patent.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.reth.2020.10.007.

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