A tissue-hybrid right ventricular pulsatile circulatory simulator with a functional tricuspid regurgitation

Jumpei Takada
Waseda University

Hayato Morimura
Waseda University

Kohei Hamada
Waseda University

Yusei Okamoto
Waseda University

Shiho Mineta
Waseda University

Yusuke Tsuboko
Waseda University

Kaoru Hattori
Waseda University

Kiyotaka Iwasaki (iwasaki@waseda.jp)
Waseda University

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Abstract

We hypothesize that the development of a pulsatile circulatory simulator with physiological morphology of tricuspid valve (TV) and right ventricle is essential to evaluate the performance after tricuspid valvuloplasty. This study aimed to develop a tissue-hybrid pulsatile circulatory simulator with clinically relevant tricuspid regurgitation (TR) to evaluate the effects of tricuspid annuloplasty. The tissue-silicone hybrid model consisted of a porcine TV sutured to a silicone right ventricular model with enlarged annulus, which can be pulsated while maintaining the relative position between the TV annulus and papillary muscle. The annulus of porcine TV was enlarged by degrading collagen fibers (pre- and post-annular perimeter 115.7 ± 5.5 vs. 133.1 ± 8.2 mm; p = 0.036). Severe TR models were successfully produced (pre- and post-regurgitation 0.64 ± 0.22 vs. 3.1 ± 0.59 L/min p = 0.0002). After the TV annuloplasty, regurgitation was reduced to a clinically mild grade (pre- and post-regurgitation 3.1 ± 0.59 vs 1.2 ± 0.27 L/min p = 0.013). The regurgitant jet in TR models was remarkably reduced after the annuloplasty. The novel tissue-hybrid system was useful to simulate severe TR and quantify the effects of the annuloplasty. The simulator would be useful to evaluate efficacy of emerging medical treatments and optimize them.

Introduction

The tricuspid valve (TV) has a unique morphology composed of three leaflets, TV annulus, the chordae tendineae connecting the leaflets, and papillary muscles located at the ventricular free wall. Functional tricuspid regurgitation (FTR) occurs primarily due to elevated right ventricular pressure, pulmonary hypertension, and tethering of leaflets. [1–3] Patients with isolated tricuspid regurgitation (TR) have been traditionally treated with palliative medical therapy to alleviate systemic congestion; however, the current guidelines on the management of valvular disease recommend early surgical intervention for patients with symptomatic severe TR to prevent irreversible right ventricle dysfunction and organ damage. [4, 5] Despite this, isolated TV surgery is rarely performed due to high rates of residual or recurrent regurgitation as well as poor postoperative outcomes (in-hospital mortality of 8–14%). [6, 7] Most surgical cases of FTR are treated using tricuspid valvuloplasty. [8] Common approaches include the use of an artificial ring to correct the TV annulus size and shape by suturing the annulus. [9, 10] The technique of TV valvuloplasty needs to be determined on the basis of preoperative geometric and dynamic parameters including TR severity, TV annular dimension, right ventricle pressures, and the extent of leaflet tethering, yet the criteria remain controversial clinically. [11–14] Therefore, the development of an experimental system to morphologically and physiologically simulate FTR is required to evaluate characteristics and performances of TV repair techniques.

In this study, we aimed to develop a pulsatile circulatory simulator incorporating a novel tissue-silicone hybrid right ventricular model with a porcine TV, annulus, and ventricular wall for simulating clinically relevant FTR and quantify the effects of a tricuspid valvuloplasty on the FTR to confirm the feasibility of the novel tissue-hybrid circulatory simulator with FTR.
Methods

Construction of a tissue-silicone hybrid right ventricular model

Twelve Porcine hearts were obtained from a local abattoir. First, the TV annulus with the right ventricular wall was trimmed from the porcine heart. The TV annulus was excised from the right atrial wall with a 10-mm seam allowance. Right ventriculotomy was limited to right ventricular outflow free wall to preserve papillary muscles and maintain the anatomical relationships of the tricuspid complex. The septal wall was trimmed to a uniform thickness consistent with that of the free wall to avoid interference with the behaviors of anterior and posterior leaflets due to its relatively excessive contraction under the external positive pressure at systole. Next, an elastic right ventricle was modeled based on geometry of 40 healthy adults [15] using a computer-aided design (CAD) software (Solidworks 2019, Dassault Systemes Solidworks Corporation, Paris, France) (Fig. 1a). CAD data were exported to a 3D printer (Eden260vs, Stratasys, Valencia, CA, USA) and modeled using a stereolithography resin (FullCure720, Altech, Tokyo, Japan). The silicone elastic right ventricular model was created using lost-wax casting (Shin-Etsu Silicone [KE-1603-A: KE-1603-B: KF-96-50CS; 10:10:8], Shin-Etsu Chemical, Tokyo, Japan) with 3-mm thickness (Fig. 1b and c). In the dilatated right ventricular model, the antero-posterior commissure of the TV annulus was dilated so that it protruded to duplicate right ventricular enlargement. The annulus perimeter and internal volume of the dilated right ventricular model were set to values 17% and 40% greater than those of the normal model, respectively, on the basis of literature values. [16, 17] The right ventricle tissues were sutured to the elastic ventricular model, and finally, the tissue-silicone hybrid right ventricle model was installed in an airtight acrylic chamber to simulate contracting and relaxing myocardium by pneumatic positive and negative pressures (Fig. 1d).

Development of a dilated annulus tissue model

The annulus tissue was treated with collagenolytic enzymes under stepwise expansion forces to induce annulus tissue degeneration and annular expansion. Considering that TV annulus is likely to dilate asymmetrically toward the commissure between the anterior and posterior leaflets [18], a dilator was designed as shown in Fig. 2a. The dilator was inserted into the TV annulus tissue (Fig. 2b) and immersed in a 0.2% collagenase solution at 37°C. The tissue with the dilator initially one size larger (2 mm larger in all directions) than the measured TV annulus size was treated in the collagenase solution for 10 minutes. Then, using the dilator with the additional 2-mm increase of the annulus size, the collagenase treatment was further conducted. Finally, the TV annulus was enlarged with the annular dilator, the size of which was increased by 6 mm in total compared to the measured TV annulus size.

Development of a tissue-hybrid right ventricular pulsatile circulatory system
The pulsatile circulatory system was composed of a porcine TV, the elastic right ventricular model incorporated in the right ventricular chamber, a bovine pericardial-made pulmonary valve, a porous resistive unit, an elastic pulmonary artery model, an elastic vena cava model, a right atrium chamber, and a pneumatic console to drive the right ventricular model (VCT-50 (χ), Nippro, Osaka, Japan) (Fig. 3). The flow through the TV was measured using an ultrasonic flow sensor (ME-PXN ME19PXN325; Transonic, NY, USA). The right atrial and ventricular pressures were measured using pressure transducers (UK-801; Baxter, CA, USA).

**Test procedures**

First, the hydrodynamics of six normal models were measured (Fig. 2c). Pressures of the systolic/diastolic right ventricle and pulmonary artery were adjusted to 20–30/0–5 mmHg and 15–30/2–8 mmHg, respectively, with a forward rate of 5.0 L/min under the conditions of heart rate, 70 beats per minute and systolic fraction, 35%. Next, six TR models (Fig. 2d) incorporated in the dilated right ventricular models were tested. Finally, the De-Vega suture annuloplasty [19] was conducted on the TR models with 4–0 sutures on the annulus overlaying anterior and posterior leaflets (Fig. 2e).

**Hydrodynamic functions**

The length of the tricuspid regurgitant jet at closing phase was measured using a cardiology ultrasound system (EPIQ CVx 3D, Philips, Amsterdam, Netherlands) to evaluate the degree of TR according to the clinical criteria. [20] Moreover, the ratio of regurgitant to forward transvalvular flow rate was calculated to quantify the effects of the suture annuloplasty on the TR.

**Statistical analysis**

Statistical analysis was performed using a software (SPSS 26, IBM, Tokyo, Japan). The forward flow rate, backflow rate, the percentage of backflow to forward flow rate, height of the regurgitant jet flow, and annulus circumference were compared among the normal model, TR model, and TV valvuloplasty model using Bonferroni method. A $p$ value lower than 0.05 was considered statistically significant.

**Results**

**Hydrodynamic measurements of the normal model**

The tissue-hybrid simulator produced physiological right ventricular and pulmonary artery pressures and tricuspid transvalvular flow (Fig. 4a and b). An echocardiography showed that the coaptation of leaflets were comparable to that of a normal human TV (Fig. 4c). Forward flow rate, regurgitant flow rate, ratio of regurgitant to forward flow rate, height of regurgitant jet, and annular perimeter (Table 1) were maintained within clinically acceptable ranges.
Table 1
Hemodynamics and morphology of Tricuspid valve models

<table>
<thead>
<tr>
<th></th>
<th>Normal model</th>
<th>TR model</th>
<th>TV Valvuloplasty model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forward flow rate [L/min]</td>
<td>4.93 ± 0.42</td>
<td>4.85 ± 0.89</td>
<td>4.63 ± 0.45</td>
</tr>
<tr>
<td>Backflow rate [L/min]</td>
<td>0.64 ± 0.22</td>
<td>3.13 ± 0.59</td>
<td>1.15 ± 0.27</td>
</tr>
<tr>
<td>Percentage of backflow to forward flow %</td>
<td>13.2 ± 1.5</td>
<td>65.4 ± 7.4</td>
<td>25.1 ± 5.5</td>
</tr>
<tr>
<td>Height of jet flow [cm]</td>
<td>1.18 ± 0.16</td>
<td>4.8 ± 0.33</td>
<td>1.33 ± 0.21</td>
</tr>
<tr>
<td>Annular circumference [mm]</td>
<td>115.7 ± 5.54</td>
<td>133.1 ± 8.2</td>
<td>111.5 ± 8.3</td>
</tr>
</tbody>
</table>

TR, tricuspid regurgitation; TV, tricuspid valve

Hemodynamic measurements of the TR model

The tissue-hybrid simulator incorporating the TR model successfully produced clinically severe TR (Fig. 5a, b and Table 1). Echocardiography showed an increase in transvalvular regurgitant flow due to the coaptation failure at closing phase in the TR model. (Fig. 5c). The backflow rate, percentage of backflow to forward flow rate, and the height of regurgitant jet flow were significantly larger in the TR model than in the normal model (backflow rate of the normal model vs. TR model: 0.64 ± 0.22 L/min vs. 3.13 ± 0.59; p = 0.0002, percentage of backflow to forward flow rate of the normal model vs. TR model: 13.2 ± 1.5% vs. 65.4 ± 7.4%; p = 0.0003, height of regurgitant jet flow of the normal model vs. TR model: 1.18 ± 0.16 cm vs. 4.8 ± 0.33 cm; p = 0.0002) (Table 1). The annular perimeter was larger in the TR model than in the normal model (perimeter of the normal model vs. TR model: 115.7 ± 5.5 mm vs. 133.1 ± 8.2 mm; p = 0.04 (Table 1). The right ventricular pressure was significantly elevated in the TR model.

Hemodynamic measurements of the TV valvuloplasty model

The flow and pressure waveforms of the tissue-hybrid simulator after the tricuspid valvuloplasty to the TR models indicated a decrease in back flow at closing phase (valvuloplasty model vs. TR model: 1.15 ± 0.27 L/min vs. 3.13 ± 0.59 L/min; p = 0.02) (Fig. 6a, b and Table 1). Echocardiography showed that the TV valvuloplasty improved leaflet’s coaptation to reduce the regurgitant jet to be considered as "mild" in a clinical setting. (Fig. 6c). The height of regurgitant jet in the TV valvuloplasty model was significantly lower than that in the TR model (valvuloplasty model vs. TR model: 1.33 ± 0.21 cm vs. 4.8 ± 0.33 cm; p = 0.0003) (Table 1). The backflow rate, percentage of backflow to forward flow rate, and annular perimeter in the TV valvuloplasty model were smaller than those of the TR model (backflow rate of the valvuloplasty model vs. TR model: 1.15 ± 0.27 L/min vs. 3.13 ± 0.59; p = 0.02, percentage of backflow to forward flow rate of the valvuloplasty model vs. TR model: 25.1 ± 5.5% vs. 65.4 ± 7.4%; p = 0.02, height of regurgitant jet flow of the valvuloplasty model vs. TR model: 1.33 ± 0.21 cm vs. 4.8 ± 0.33 cm; p = 0.0003) (Table 1). The backflow rate and the percentage of backflow to forward flow rate in the TV valvuloplasty...
model did not recover to those in the normal model (backflow rate of the valvuloplasty model vs. normal model: 1.15 ± 0.27 L/min vs. 0.64 ± 0.22; p = 0.01, percentage of backflow to forward flow rate of the valvuloplasty model vs. normal model: 25.1 ± 5.5% vs. 13.2 ± 1.5%; p = 0.02) (Table 1). The present results quantitatively demonstrated the efficacy of the tricuspid valvuloplasty on severe regurgitation due to dilated annulus in the TR model.

Discussion

In this study, we successfully developed a novel tissue-hybrid right ventricular circulatory system incorporating the porcine TVs, which maintained the relative positioning between the TV annulus and papillary muscle. The tissue-hybrid circulatory system could produce physiological flow and pressure environments. We also devised a dilated TV model by treating the valve annulus with collagenolytic enzymes under stepwise expansion and could produce a clinically relevant TR. Moreover, using the hybrid simulator incorporating the TR model, we could quantitatively evaluate the effects of tricuspid annuloplasty on the reduction of regurgitation as well as the improvement of leaflets' coaptation.

To the best of our knowledge, this is the first report on an experimental model that morphologically and dynamically simulates FTR, in which the three parameters that may affect the outcomes of TV repair are adjustable: annular size, right ventricular pressure, and right ventricular volume as a determinant of the leaflet tethering height. Leaflet tethering of TV, which results from displacement of the papillary muscle due to altered right ventricle geometry, has been reported as an independent predictive of residual regurgitation early after TV annuloplasty. [14] Current annuloplasty techniques are not recommended to treat TR with severe tethering, and additional repair techniques that correct both annular dilatation and leaflet tethering are often required. [21] In contrast, the degree of annular dilatation is less likely to affect the surgical outcomes. [14] Transcatheter and less invasive surgical approaches for TV annuloplasty may be feasible and safe options for patients with TR with simple annular dilatation; the development of these less invasive techniques may result in early surgical intervention and improving treatment outcomes in patients with symptomatic TR at high-risk. [22] We believe that the hybrid right ventricular circulatory simulator may contribute not only to improve surgical techniques of TV valvuloplasty, but also to speed up the development of treatment devices including new-styled prosthesis, annular rings, and catheter-based devices.

There have been several reports on the in vitro test system with TV. [23–25, 22] In previous studies, TVs were incorporated directly into the simulator or the animal hearts were used. However, these studies have three issues: (1) because the papillary muscles do not displace with beating, the model cannot duplicate the dynamic leaflet's behavior of the TV, (2) animal hearts cannot reproduce the FTR state, and (3) the geometry of the healthy animal right ventricle differs from that of the human dilated right ventricle. In the present study, a right ventricular simulator incorporating a novel tissue-hybrid right ventricular model was developed. In this simulator, the anatomical relationships of the “tricuspid complex” that consists of tricuspid annulus, chordae tendineae, papillary muscle, and ventricle wall were maintained morphologically relevant to the dilated human heart, and the efficacy of annuloplasty for FTR with
annular dilatation could be quantified. In future studies, using the present experimental system, we will examine the characteristics of FTR with different severity and pathology, particularly with higher right ventricular pressure, larger right ventricle volume, or smaller tethering height of leaflets, which are considered negative indexes to surgical outcomes. We believe that the thorough assessment of the effects of the tricuspid surgical treatments in pathological models may contribute to proper and effective choices of surgical treatments and optimizing them.

This study had some limitations. First, in our right ventricular model, the free wall and septum models deform in the same manner because the drive pressure acts evenly to the outside surface of the right ventricular model. In humans, the right ventricular free wall contracts and dilates predominantly, and the septum does not deform. In a future study, we will attempt to develop an elastic right ventricular model with behaviors equivalent to those of humans by devising a constraint to restrain movement of the septal side. Second, in the present study, the effects of TV annuloplasty could be evaluated only in the intraoperative phase when the remodeling effects of the right ventricle were absent. A study assessing the correlation between the experimental data using the present model and clinical findings of mid-term follow-ups may contribute to the mid-term prediction of surgical outcomes. We aim to develop a remodeled right ventricular model using clinical data of magnetic resonance imaging or computed tomography in the chronic phase after TV surgery to evaluate the effects of TR correction on mid-term hemodynamics after right ventricle remodeling in the future.

Conclusions

We successfully developed a right ventricular circulatory simulator that duplicated the physiological flow and pressure environments of the TV by devising a novel tissue-silicone hybrid right ventricular model incorporating porcine TVs, annulus, and ventricular wall, which could maintain the relative positioning between the TV annulus and papillary muscle. Moreover, we devised a method to dilate TV annulus by treating with collagenolytic enzymes under the three-step expansion and generated clinically relevant TR. The feasibility of the tissue-hybrid simulator incorporating the TR model was confirmed by the quantitative assessments of the effects of the tricuspid annuloplasty on the reduction of the regurgitation as well as the improvement of the leaflets’ coaptation. The hybrid circulatory simulator may contribute to proper and effective choices of surgical treatments and expedite the development of catheter-based less invasive devices.

Declarations

Acknowledgements

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Author contributions

J.T. conceptualized, designed the study, performed the experiments, analyzed the data, and wrote the original draft. H.M., K.H., Y.O., S.M., Y.T., and K.H. performed the experiments and analyzed the data. K.I.
conceptualized and designed the study, interpreted, critically revised the original draft, and supervised.

Data availability statement

The datasets generated and/or analyzed during the current study are not publicly available due to no public text sources but are available from the corresponding author on reasonable request.

Competing interest statement

The authors declare no competing interests.

References


**Figures**
Figure 1

The method for constructing tissue-silicone hybrid model. a: Computer-Aided design model, b: The gap between the outer frame and the lumen models, c: An elastic right ventricular model, d: A model incorporated in the acrylic chamber.
Figure 2

The device to produce the tricuspid regurgitation model. a: A dilation component, b: Method to insert a dilation component, c: Normal tissue-silicone hybrid model, d: Functional tricuspid regurgitation tissue-silicone hybrid model, e: Valvuloplasty on tissue-silicone hybrid model.
Figure 3

A tissue-hybrid pulsatile right ventricular circulatory system
Figure 4

Hemodynamics of the normal model. a: Pressure waveform, b: Flow waveform, c: Transvalvular jet flow at the valve closure.
Figure 5

Hemodynamics of the regurgitant model. a: Pressure waveform, b: Flow waveform, c: Transvalvular jet flow at the valve closure.
Figure 6

Hemodynamics of the valvuloplasty model. a: Pressure waveform, b: Flow waveform, c: Transvalvular jet flow at the valve closure.