

## A novel method to reduce pericardial adhesion: A combination technique with hyaluronic acid biocompatible membrane

Yuji Naito, MD, Toshiharu Shin'oka, MD, PhD, Narutoshi Hibino, MD, PhD, Goki Matsumura, MD, PhD, and Hiromi Kurosawa, MD, PhD

**Objective:** This study was to evaluate the efficacy of the hyaluronic acid (HA) bioabsorbable membrane combined use with both expanded-polytetrafluoroethylene (ePTFE) and autologous pericardium for preventing postoperative pericardial adhesions.

**Methods:** The HA bioresorbable surgical membrane (Septrafilm, Genzyme, Cambridge, Mass) was used with either ePTFE or autologous pericardium in an experimental pericardial adhesion model. Twenty-four beagle dogs were classified as follows; Group A (n = 6): ePTFE only, Group B (n = 6): Septrafilm + ePTFE, Group C (n = 6): autologous pericardium only, Group D (n = 6): Septrafilm + autologous pericardium. Pericardial adhesions were evaluated at necropsy at 4, 8, and 12 weeks. The tenacity of adhesion was graded by macroscopic examination, and the adhesion tissue thickness was analyzed microscopically with an image processing program. The regeneration of mesothelial cells on neo-tissue fibrils were immunohistochemically studied.

**Results:** In groups B and D, the adhesions were significant lower compared with those of control groups in the tenacity (Group A vs B:  $2.5 \pm 0.55$  vs  $1.5 \pm 0.55$ ,  $P < 0.05$ ; Group C vs D:  $3.2 \pm 0.75$  vs  $0.33 \pm 0.52$ ,  $P < 0.01$ ) and the tissue thickness (Group A vs B:  $30.4 \pm 12.9$  vs  $10.3 \pm 4.42$ ,  $P < 0.01$ ; Group C vs D:  $22.6 \pm 11.5$  vs  $4.96 \pm 4.87$ ,  $P < 0.01$ ). Immunohistochemically, a single layer of mesothelial cells were regenerated on the surface of neo-tissue fibrils in HA treated groups.

**Conclusion:** The combined use of Septrafilm with either ePTFE or autologous pericardium effectively reduced the formation of pericardial adhesion.

At the time of reoperation in cardiac surgery, injury to the heart, great vessels, and any aorta–coronary bypass graft results in severe hemorrhage with significant morbidity and mortality.<sup>1</sup> In congenital heart disease, patients with univentricular physiology undergo several surgical procedures during the first years of life.<sup>2</sup> Others, patients with right ventricle–pulmonary artery conduit, may require reoperation for conduit stenosis or insufficiency later in life. Although the number of patients was limited, reoperation is inevitable in adult cardiac surgery for ischemic heart disease and valvular heart disease. Any reoperation in congenital or adult cardiac surgery imposes an increased surgical risk onto the individual patient.<sup>3</sup> This increased risk is mostly caused by the occurrence of surgical adhesions.

From the Heart Institute of Japan, Department of Cardiovascular Surgery, Tokyo Women's Medical University, Tokyo, Japan.

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Address for reprints: Yuji Naito, MD; Heart Institute of Japan, Department of Cardiovascular Surgery, Tokyo Women's Medical University, 8-1 Kawada-cho Shinjyuku-ku, Tokyo, 162-8666 Japan (E-mail: [ujinaito@aol.com](mailto:ujinaito@aol.com)).

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### Abbreviations and Acronyms

ANOVA	= analysis of variance
ePTFE	= expanded polytetrafluoroethylene
HA	= hyaluronic acid
NTF	= neotissue fibrils
PLSD	= protected least significant difference

This problem is especially serious in children because it is technically difficult to establish extracorporeal circulation by cannulating the femoral vessels.

Despite continuous research over the decades, an ideal method to prevent postoperative pericardial adhesion formation has not been found so far. Pericardial reconstruction with expanded polytetrafluoroethylene (ePTFE) has demonstrated more success<sup>4</sup> but also has been reported to induce severe constrictive pericardial adhesions.<sup>5,6</sup> The natural biopolymer, hyaluronic acid (HA), reduces adhesion formation in abdominal surgery.<sup>7-9</sup> Recently, an acceptable clinical result of HA membrane for reduction of postoperative adhesion in pediatric heart surgery was observed.<sup>10</sup>

In this study, we describe the use of the HA bioabsorbable membrane combined with both ePTFE and autologous pericardium in prevention of postoperative pericardial adhesion in a canine model.

## Material and Methods

### Antiadhesive Membrane

The HA bioresorbable membrane (Septrafilm, Genzyme, Cambridge, Mass), which was composed of sodium hyaluronate and carboxymethylcellulose, was used in this study. The size of the membrane was approximately 5 × 5 cm. The membrane was brought out from the holder and applied to the intended area.

### Animal Preparation

The Animal Care and Use Committee of Tokyo Women's Medical University approved the use of the animals. All animals received human care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research, and the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication 85-23, revised in 1996).

Twenty-four beagle dogs weighing 9.1 to 12.5 kg were used in this study. The animals were classified as follows by method of pericardial reconstruction.

In group A (n = 6), an ePTFE (Gore-Tex pericardial membrane; W. L. Gore & Associates, Inc, Flagstaff, Ariz) elliptic patch about 20 × 30 mm was used to cover the pericardial defect by continuous 6-0 Prolene sutures (Ethicon, Inc, Somerville, NJ). In group B (n = 6), after the HA bioresorbable membrane covered the epicardium, ePTFE was placed to close the defect. In group C (n = 6), the pericardium was simply closed with no artificial materials. In group D, the HA bioresorbable membrane covered the epicardium before pericardial closure.

## Operation

General anesthesia was induced by intravenous injection of sodium pentobarbital (25 mg/kg) followed immediately by endotracheal intubation; anesthesia was maintained by additional intravenous injections of sodium pentobarbital (5 mg/kg). With the use of an aseptic technique, a thoracotomy was performed through the fourth or fifth intercostal space. Pericardium was opened longitudinally about 3 cm in length, and the exposed epicardial surfaces of the right ventricular outflow tract were desiccated and abraded for 3 minutes with gauze. In groups A and B, the pericardium was resected about the size of ePTFE patch. Then pericardium was closed according to the method of pericardial reconstruction with nonabsorbable monofilament fiber with blood contained in the intrapericardial cavity. A thoracic drain was placed to evacuate the thoracic cavity, and the chest was closed in 3 layers with nonabsorbable sutures. Subsequently, after complete suction, the thoracic drain was removed.

## Macroscopic Evaluation

In each group, every 2 animals underwent rethoracotomy 4, 8, or 12 weeks after the initial procedure, respectively. Intrapericardial adhesions were scored by an observer blinded to the experimental groups, according to the severity of adhesion; 0, no adhesion; 1, mild adhesion (easy to dissect manually); 2, moderate adhesion (cohesive and can be dissected manually); 3, severe adhesion (cohesive, requires sharp dissection); 4, undissectable (bleeding occurred from the heart).

## Microscopic Evaluation

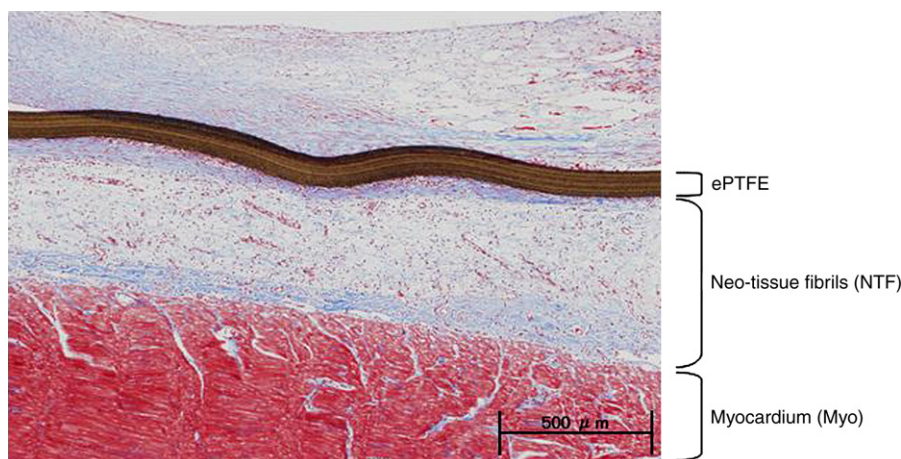
After macroscopic examination, the animals were humanely killed, and both the myocardium of the right ventricular outflow tract and the pericardial tissue were explanted en bloc. For the light microscopic evaluation, the specimens were fixed in 10% phosphate-buffered formalin and cut into segments containing the adhesive parts. The suture line in the explanted tissue represents the zone of contact with the native pericardial tissue or the ePTFE. If the corresponding piece of native pericardial tissue was not adhesive to myocardium, it was also explanted. All the specimens were embedded in paraffin. Each tissue was stained with hematoxylin-eosin and Masson trichrome stain, and the microscopic evaluation was performed to measure the extent of fibrosis.

## Immunohistochemical Analysis of Mesothelial Cells

Additional sections of the specimens were also stained with immunohistochemical techniques by using monoclonal antibodies against HBME-1 (DAKO Corporation, Carpinteria, Calif) to identify mesothelial cell.

## Adhesion Tissue Thickness Analysis With Image Processing Program

The neotissue fibrils (NTF), which consisted of dense collagen fiber, could be distinguished microscopically from myocardium and adipose tissue in Masson trichrome stain (Figure 1). The image of each tissue of 100 magnification was analyzed with the National Institutes of Health Image program (version 1.62; National Institutes of Health, Springfield, Va), and the area of adhesion tissue was calculated as the adhesion tissue thickness.



**Figure 1.** The adhesion tissue thickness analysis. The neotissue fibrils, which consist of dense collagenous fiber, could be distinguished from myocardium microscopically in Masson trichrome stain. The image of each tissue was analyzed by National Institutes of Health image, and the area of adhesion tissue was calculated. *ePTFE*, Expanded polytetrafluoroethylene.

**Statistics**

All statistical analyses were performed by SPSS for Windows, version 11.5 (SPSS Inc, Chicago, Ill). All data are presented as mean ± SD. Normally distributed data were compared by the Student *t* test and 1-way analysis of variance. The nonparametric Mann–Whitney *U* test and Kruskal–Wallis test were conducted to compare the difference if the data were not normal distribution. The post hoc tests were conducted as multiple comparisons with either the Fisher protected least significant difference (PLSD) test or the Scheffé test according to the distribution of data.

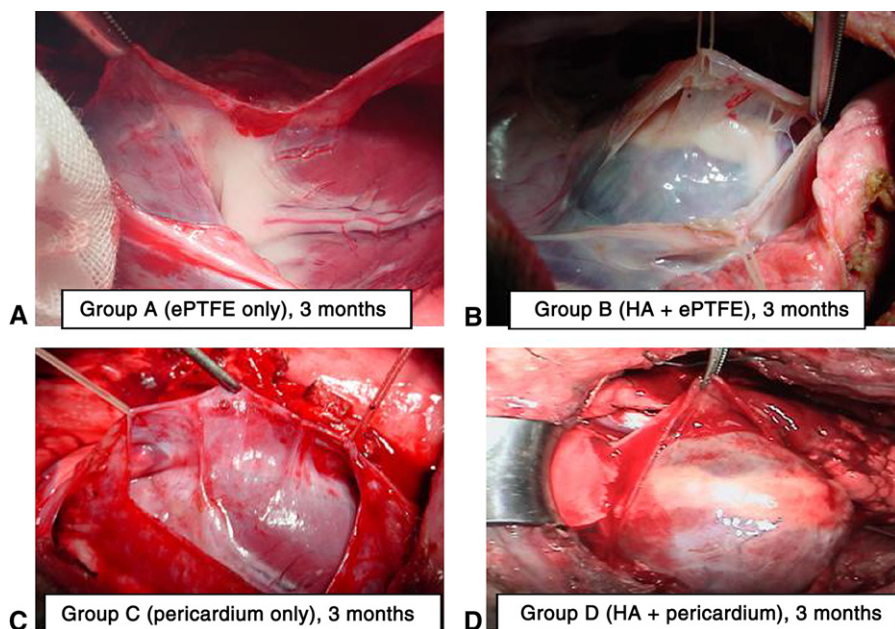
**Results**

All animals tolerated the procedure with no apparent postoperative complications. Clinical follow-up over 3 months did not reveal any abnormalities except for a superficial wound infection. The HA significantly reduced the adhesion tenacity

score in groups B and D ( $P < .05$  and  $P < .01$ , respectively, by Mann–Whitney *U* test) compared with control groups, and the adhesion tissue thickness was significantly lower in groups B and D ( $P < .01$  in both groups by the Student *t* test) than in the control groups (Table 1).

**Macroscopic Examination**

In group A, the control animals, moderate-to-severe tenacious adhesions were observed between the epicardium and the ePTFE patch, and the edges of the epicardium were intimately adherent to both the pericardium and ePTFE and extremely difficult to dissect out (Figure 2, A). In contrast, the adhesion formation in group B, the HA-treated group, was extremely low. A smooth pericardium-like membrane was observed and several fibrous strands were formed between ePTFE and epicardium, which facilitated a quick



**Figure 2.** Three months after the initial operation, moderate-to-severe tenacious adhesions were observed between the epicardium and the ePTFE patch in group A (A), whereas the adhesion formation in group B was extremely low, with several fibrous strands formed on the epicardial surface (B). In group C, marked adhesion formation, which was difficult to dissect out, was observed in the pericardial cavity (C). In group D, almost no adhesion was formed in the pericardial cavity, and the epicardium was almost intact, which made the coronary vessels clearly identifiable (D).

**TABLE 1. Evaluation with adhesion tenacity scores and adhesion tissue thickness**

Groups	Duration to planned death	Adhesion tenacity score	Adhesion tissue thickness
A (control)	4 wk	2	22.4
	4 wk	3	34.5
	8 wk	2	21.8
	8 wk	3	28.5
	12 wk	3	54.5
	12 wk	2	20.9
Mean ± SD		2.5 ± 0.55	30.4 ± 12.9
B (HA treated)	4 wk	2	6.38
	4 wk	1	9.11
	8 wk	2	17.4
	8 wk	2	13.2
	12 wk	1	5.65
	12 wk	1	9.8
		1.5* ± 0.55	10.3‡ ± 4.42
C (control)	4 wk	3	14.9
	4 wk	4	34.1
	8 wk	2	9.61
	8 wk	3	26.5
	12 wk	3	13.5
	12 wk	4	9.8
		3.2 ± 0.75	22.6 ± 11.5
D (HA treated)	4 wk	0	2.41
	4 wk	0	1.11
	8 wk	1	12.6
	8 wk	0	2.45
	12 wk	1	9.59
	12 wk	0	1.62
		0.3‡ ± 0.52	4.96‡ ± 4.87

SD, Standard deviation; HA, hyaluronic acid. \**P* < .05. †*P* < .01 versus control by Mann–Whitney *U* test. ‡*P* < .01 versus control by Student *t* test.

and easy dissection between the epicardium and ePTFE (Figure 2, B).

In group C, marked adhesions between epicardium and pericardium were observed, and the adhesions in this group were so tenacious that the pericardial tissue could not be sep-

arated from the heart without damaging the myocardial tissue (Figure 2, C). As was observed in group B, the adhesion formation in group D, the HA-treated group, was extremely low. Almost no adhesion was formed in the pericardial cavity, and the epicardium was almost intact, which made the coronary vessels clearly identifiable (Figure 2, D).

There was a significant difference of the mean tenacity score of adhesion in the studied groups (*P* < .05, by Kruskal–Wallis test), and group D showed a significantly lower score of adhesion than other groups (D vs A, *P* < .01; D vs B, *P* < .05; D vs C, *P* < .01; respectively, by the Scheffé test) (Figure 3, A).

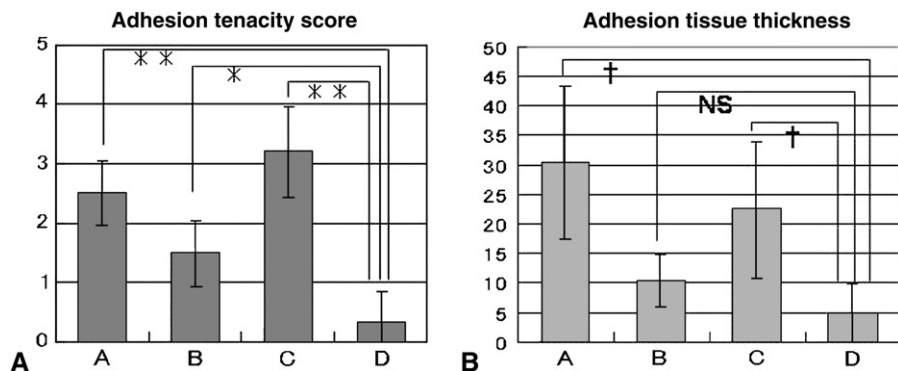
**Microscopic Examination**

All specimens consisted of a mesothelium-like lining, NTF, myocardium, and adipose tissue. In group A, a thick layer of NTF that consisted of collagen fiber was observed between ePTFE and epicardium. These findings were in direct agreement with those observed at macroscopic examinations (Figure 4, A). In group B, the surface of NTF on the ePTFE sheet was covered with a mesothelium-like lining (Figure 4, B1), under which there was a layer of fibrous tissue with a population of fibroblast (Figure 4, B2). In group C, a moderately thick layer of NTF was noted between the epicardium and pericardium, and small arteries or blood capillaries had developed in the NTF (Figure 4, C). In group D, a very thin layer of NTF was formed on the surface of epicardium (Figure 4, D1), and it was covered with a mesothelium-like lining as was observed in group B (Figure 4, D2).

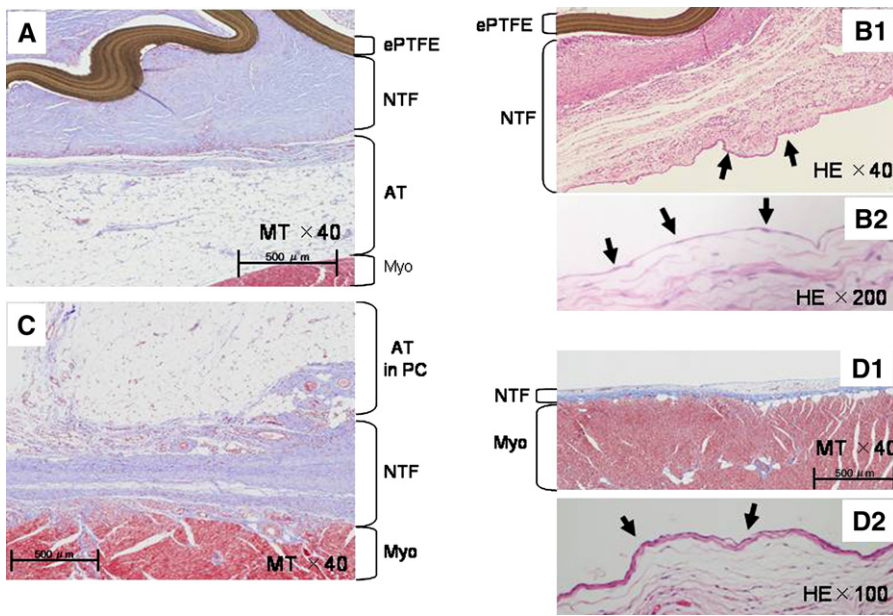
There was a significant difference in the mean adhesion tissue thickness in the studied groups (*P* < .01, by 1-way analysis of variance). Group D showed significantly less tissue thickness than groups A and C (D vs A, *P* < .01; D vs C, *P* < .01, respectively, by the Fisher PLSD test), whereas, the difference between groups B and D was not statistically significant (*P* = .097 by the Fisher PLSD test) (Figure 3, B).

**Immunohistochemical Study**

Group D showed a single layer of mesothelial cells lining the whole surface of NTF on the epicardium (Figure 5, A). In



**Figure 3. Mean adhesion tenacity score (A) and mean adhesion tissue thickness (B). \**P* < .05, \*\**P* < .01, respectively, by the Scheffé test. †*P* < .01 by the Fisher PLSD test.**



**Figure 4.** In group A, a thick layer of neotissue fibrils (NTF) was observed between expanded polytetrafluoroethylene (ePTFE) and epicardium (A). In group B, the surface of NTF on ePTFE sheet was covered with a mesothelium-like lining (arrows) (B1, B2). In group C, a moderately thick layer of NTF with small arteries was noted between the epicardium and pericardium (C). In contrast, a very thin layer of epicardium was formed on the surface of epicardium in group D (D1). A mesothelium-like lining (arrows) was identified on the surface of NTF (D2). AT, Adipose tissue; AT in PC, adipose tissue in pericardium; Myo, myocardium; HE, Hematoxylin–eosin stain; MT, Masson trichrome stain.

group B, several mesothelial cell linings on NTF were regenerated on the ePTFE patch in the same way as in group D (Figure 5, B).

**Discussion**

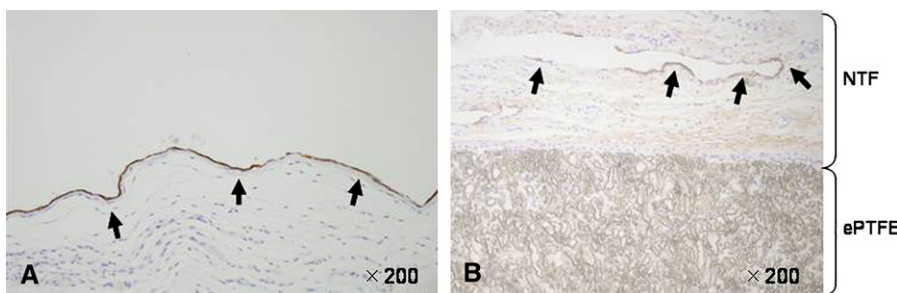
**Mechanism of Postoperative Adhesion Formation**

Histologic examination of peritoneal tissue obtained from animals undergoing abdominal surgical procedures indicates that damage to the mesothelium caused by ischemia, trauma, or infection is adhesiogenic.<sup>11</sup> As regards pericardium, the presence of both blood and serosal injury has been identified as necessary for adhesion development.<sup>12</sup> Leak and associates<sup>13</sup> examined the temporal changes in an experimental model of pericarditis with subsequent adhesion formation and discussed the 4 steps of adhesion formation: (1) the exudation of fluid, inflammatory cells, and fibrin (in 24 hours), (2) desquamation of injured mesothelial cells with aggregation of inflammatory cells to the mesothelial surfaces and fibrin deposition (in 72 hours), (3) fibrinolysis and collagen deposition with the growth of new blood and lymphatic vessels into new connective tissue (in a week), and (4) development of focal adhesions (in 2 weeks).

**Current Reported Methods for Prevention of Postoperative Adhesions**

A large number of investigations for preventing postoperative adhesions were conducted, but optimal methods to prevent adhesions are not available at present.

1. *PTFE.* A survey was conducted among cardiac surgeons to gather information on experience with the use of pericardial substitutes. The findings at reoperation showed the experience with ePTFE pericardial substitutes to be satisfactory.<sup>14</sup> Loebe and associates<sup>15</sup> described their clinical use of ePTFE surgical membrane in congenital heart disease, finding its use for pericardial closure in children to be safe for preventing complications at reoperation.
2. *Silicone.* Several groups attempted to use silicone as a pericardial substitute for prevention of adhesion.<sup>16,17</sup> Laks, Hammond, and Geha<sup>18</sup> reported their experience with silicone rubber as pericardial substitute in both adult and pediatric cardiac operations. They concluded that the silicone rubber greatly facilitated opening of the sternum but did not have help to prevent adhesion formation within the pericardium.



**Figure 5.** Immunohistochemically stained mesothelial cells. In group D, a single layer of mesothelial cell lining (arrows) on the whole surface of neotissue fibrils (NTF) was observed (A). In group B, several mesothelial cell linings (arrows) on NTF were recognized in the same way as group D (B). ePTFE, Expanded polytetrafluoroethylene.

3. *Xenograft*. Bovine pericardium was tested for preventing pericardial adhesions with excellent results.<sup>5</sup> In the clinical setting, however, bovine pericardium used as pericardial substitute was reported to cause several complications.<sup>19</sup>
4. *Absorbable polymer*. Several experimental studies have been conducted to reduce postoperative adhesion formation with biocompatible absorbable membrane,<sup>20-22</sup> but none of these materials has been applied in the clinical setting so far.
5. *Prevention of fibrinogenesis*. In the pathogenesis of adhesion formation, an imbalance between fibrin deposition and fibrin dissolution is the key event.<sup>23</sup> Pericardial adhesions were believed to form in consequence of impaired pericardial fibrinolytic activity. The several fibrinolytic agents were reported to reduce postoperative pericardial adhesion in a rabbit model. However, further work is required to assess their safety in terms of bleeding or altered healing before they are used clinically.<sup>24</sup>
6. *HA biocompatible membrane*. The efficacy of HA to prevent postoperative adhesions was demonstrated in various surgical fields involving cardiovascular surgery. Pericardial tissue surfaces are known to possess inherent fibrinolytic activity that is reduced after mesothelial damage has occurred,<sup>25</sup> particularly when cardiopulmonary bypass is used.<sup>26</sup> Fibrinolytic activity in the pericardial cavity is resumed significantly by the sixth day after injury.<sup>13</sup> Until mesothelial healing occurs, the presence of a nonreactive barrier that blocks the contact between the damaged pericardial surface and surrounding tissue could prevent significant postoperative adhesion.

### **Benefit of Combined Use of HA With Either ePTFE or Autologous Pericardium**

In the majority of patients with congenital heart disease, autologous pericardium is excised to be used for surgical corrections (eg, right ventricular outflow tract patch enlargement, atrioventricular septal defect repair). Meanwhile, direct closure of the autologous pericardium is possible in a small number of young patients with single ventricular physiology when they undergo either pulmonary artery banding or bidirectional Glenn anastomosis. Although the number of patients was limited, reoperation is inevitable in adult cardiac surgery for ischemic heart disease and valvular heart disease where direct closure of autologous pericardium is feasible. Considering results of prevention of postoperative adhesion formation, combined use of HA with ePTFE was a reasonable method in that both measures were currently in clinical use and showed acceptable results. Our results showed significant low tenacity scores of adhesion in group D, whereas there was no statistically significant difference between groups B and D as regards adhesion tissue

thickness, which might support the beneficial effect of combined use of HA with ePTFE.

HA biocompatible membrane becomes a gel in 24 to 48 hours after application to organ surfaces and stays unabsorbed for approximately 7 days in the peritoneal cavity, which results in a physical barrier against surrounding tissue to prevent adhesion formation.<sup>7</sup> The persistence time of HA membrane in the pericardial space is unknown, although it would partially prevent the aggregation of inflammatory cells and fibrin deposition to the mesothelial surfaces, which occurs in 72 hours after mesothelial injury according to Leak's theory.<sup>13</sup> If the foreign material was used in the pericardial space, inflammatory response would occur to some extent, which results in the formation of NTF; however, the noncontacted area created by HA gel would prevent the NTF overgrowth to form several cavities between the foreign material and the epicardium. Additionally, use of biocompatible material would contribute to preclude the foreign body reaction seen with permanently implanted devices.

In the HA-treated groups, we were surprised to find that a single layer of mesothelial cells was regenerated on NTF, which implies long-term effect against adhesion formation in that mesothelial cells retain fibrinolytic function. The HA was one of the major structural components of the extracellular matrix. The extracellular matrix is known to serve several functions in controlling cell behaviors, such as adhesion, growth, proliferation, and migration.<sup>27</sup> The HA was reported to be involved in cell proliferation and haptotaxis in mesothelial cell lineage.<sup>28</sup> We speculated that the HA had a beneficial effect on mesothelial cell migration, adhesion, and proliferation on the surface of NTF.

### **Limitation of the Study**

The experimental results could not be completely reproducible clinically because the median sternotomy model was not used, the induction of adhesion in this study was limited, cardiopulmonary bypass was not performed, bleeding was minimal, crystalloid rinsing of the chest was not performed, and the subjects were not cyanotic. In current cardiac surgery, reoperations within a 3-month period are infrequent, and the follow-up period of 3 months is short. Further experiments with longer observation periods are necessary to elucidate the issue.

### **Conclusions**

In pericardial reconstruction with either ePTFE or autologous pericardium, the HA biocompatible membrane significantly reduced postoperative pericardial adhesion.

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### Notice of Correction

Wolf PS, Merry HE, Farivar AS, McCourtie, Mulligan MS. Stress-activated protein kinase inhibition to ameliorate lung ischemia reperfusion injury. *J Thorac Cardiovasc Surg.* 2008;135:656-65.

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