ANIMAL STUDY SERIES IN BIORESORBABLE TECHNOLOGY

Evaluation of Bioresorbable PLA Film For the Reduction of Pericardial and Retrosternal Adhesions in a Large Animal Model

J. Iliopoulos, MBBS[†]
G.B. Cornwall, PhD, PEng*
R. Evans, MD, MSc, FRCS[†]
K.A.Thomas, PhD*
C. Manganas, MBBS, FRACS[††]
D. Newman, MBBS, FRACS[††]
W.R. Walsh, PhD[†]

[†]Orthopaedic Research Laboratories
[††]Division of Surgery University of New South Wales Prince of Wales Hospital
Sydney, Australia

ABSTRACT

A large animal (swine) model was used to evaluate pericardial and retrosternal adhesions. With a mini-sternotomy, a pericardial defect was created to simulate harvesting of the pericardium with a 2 cm gap between repaired pericardial surfaces. A bioresorbable PLA film, SurgiWrap®(MAST Biosurgery, San Diego, CA), was evaluated with two different thicknesses: 0.02mm (thin) and 0.05mm (thick). Also, two different placement strategies were employed – the first with the film tucked between the pericardium and the heart. The second placement strategy was to place the film between the sternotomy and the pericardium in combination with the film placed between the pericardium and the heart. After a four-week survival period, the ability to access the anatomy through a surgical dissection plane was evaluated using a zero to three-point scale. Also, the adhesions in various locations around the heart and in particular at the sternal surgical site were evaluated with a zero to five-point scale. The resorbable adhesion barrier film was found to provide an effective surgical dissection plane between the sternum and the pericardium, and also between the pericardium and the heart.

INTRODUCTION

Retrosternal and intrapericardial adhesions following median sternotomy are a significant cause of morbidity and mortality (Loop, 1984; Dobell & Jain, 1984). The presence of pericardial adhesions at reoperation is associated with increased risk of injury to the heart, great vessels, and extra cardiac grafts. Dissection through the adhesions increases the operative time (Loop, 1984), and can significantly impact the clinical outcome, physiologic function (Bailey et al., 1984) and economic aspects of the procedure.

The prophylactic uses of various biomaterials have been evaluated to prevent or minimize the development of postoperative adhesions after cardiac surgery. Materials studied have included hydrophilic polymer solutions (Duncan et al., 1988), hydrogels (Krause et al., 2001), fibrin sealants (Boris et al., 1996; Moro et al., 1999; Wiseman et al., 1992) and polymeric membranes (Duncan et al., 1988; Malm et al., 1992; Hendrikx et al., 2001; Okuyama et al., 1998; Okuyama et al., 1999; Seeger et al., 1997).

A variety of animal models have been used in these studies including:

- Rabbits (Hioki et al., 1998; Krause et al., 2001 Hendrikx et al., 2001; Okuyama et al., 1998; Robison et al., 1984; Wiseman et al., 1992)
- Dogs (Okuyama et al., 1999; Pacholewicz et al., 1994; Seeger et al., 1997)
- Sheep (Bunton et al., 1990; Duvernoy et al., 1995; Malm et al., 1992)
- Pigs (Boris et al., 1996; Joyce et al., 1991; Moro et al., 1999)

We used a pig model of retrosternal adhesion formation via an inferior hemisternotomy to evaluate the formation of pericardial and retrosternal adhesions as well as their prevention using two different thicknesses of a bioresorbable polylactide film.

MATERIALS AND METHODS

Study Design

Adult female pigs (70 kg) were used in accordance with institutional ethics approval. Animals were allocated to either a control group or to one of four treatment groups. Two thicknesses of a bioresorbable PLA film were evaluated, 0.02mm and 0.05mm thick. The film was placed either inside the pericardium or inside and outside the pericardium,

TABLE 1. **Study Design**

Groups	Number of Animals	Time Point
1: Control	5	4 weeks
2: 0.02 mm film inside the pericardium	5	4 weeks
3: 0.02 mm film inside and outside the pericardium	5	4 weeks
4: 0.05 mm film inside the pericardium	5	4 weeks
5: 0.05 mm film inside and outside the pericardium	5	4 weeks

as outlined in Table 1. The bioresorbable PLA film is an amorphous copolymer of Poly (L-lactide-co-D,L-lactide) sterilized by electron-beam irradiation.

Polylactide is a bioresorbable material which is degraded by hydrolytic scission (bulk hydrolysis) at the implant site, followed by metabolism in the tricarboxylic acid cycle in the liver. The end products of polylactide degradation are carbon dioxide and water. Bulk forms (sheets, plates, screws) of the material require approximately 18-36 months for resorption. The estimation for ultimate resorption of the bioresorbable PLA film in the human body is a period of 9-18 months.

Surgical Procedure

Anaesthesia was induced with intramuscular injection of Ketamine (10-15 mg/kg), followed by spraying of the vocal cords with lignocaine and endotracheal intubation. Anaesthesia was maintained with halothane and oxygen. Temgesic was used for analgesia. Intravenous Cephalozin was used for antibiotic prophylaxis (1 gram). The animal was positioned supine, the operative site was marked, and the skin prepped and draped in a sterile manner. The surgeons wore powder-free gloves to avoid any contamination due to talc.

A skin incision was made in the midline extending from the middle of the sternum to just below the xiphisternum, inferiorly. The soft tissues were divided using electrocautery, and the xiphisternum divided using scissors. The retrosternal space was dissected inferiorly using blunt finger dissection. The periosteum was marked using electrocautery and the inferior half of the sternum divided in the midline using an oscillating saw. The cut sternal edges were displaced using a sternal retractor. The fibrous pericardium was divided in the midline, longitudinally with an incision measuring approximately 8 cm. The anterior surface of the heart was abraded using 30 controlled firm strokes with surgical 4 by 4 gauze (Okuyama et al., 1998). The pericardial space was infused with 50ml of sterile saline.

Following the treatment, if any, the pericardium was loosely apposed using 2 interrupted 3-0 Dexon sutures (Davis and Geck, North Ryde, AU) to form a pericardial window 2 cm in width in all animals as illustrated in Figure 1. The inferior hemisternotomy was closed using two interrupted sternal wires (Ethicon Surgical, North Ryde, AU) followed by closure of the soft tissue and skin in layers 3-0 Dexon (Davis and Geck, North Ryde, AU). Chest drains were not used.

Treatments

No material was used in the control group of animals. In Groups 2 and 4, an approximately 75 by 100mm piece of either 0.02mm or 0.05mm thick bioresorbable PLA film was placed underneath the pericardium adjacent to the anterior surface of the heart prior to apposition closure of the pericardium (Table 1). No suture was used to fix the film in place. In Groups 3 and 5 an approximately 75 by 100mm piece of either 0.02mm or 0.05mm thick bioresorbable PLA film was placed underneath the pericardium adjacent to the anterior surface of the heart prior to apposition closure of the pericardium. A second layer of the same thickness of film, measuring 100 by 130mm, was placed inferior to the sternum and superior to the pericardium. No suture was used to fix either piece of film in place.

Recovery

Animals were recovered and monitored daily during the first seven postoperative days. All pigs received

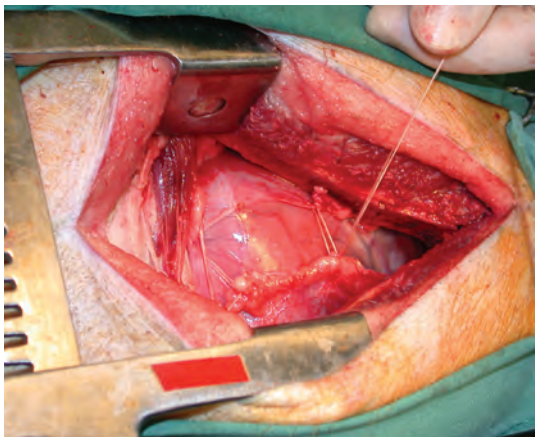

FIGURE 1.
Photograph of surgical technique illustrating hemi-sternotomy, and placement of film underneath the pericardium adjacent to the heart and suture placed to control the gap between opposing pericardial surfaces.

TABLE 2. **Adhesion Grading Scale**

Locations Evaluated Between the Pericardium and the Myocardium
Region A: posterior aspect of the heart
Region B: lateral, left side of the heart
Region C: lateral, right side of the heart
Region D: anterior aspect of the heart, inferior (surgical site)

Location Evaluated Between the Pericardium and the Sternum
Region E: anterior aspect of the heart, retrosternal

Scale Used for All Regions
0 = no adhesions
1 = sparse, can easily dissect manually, focal
2 = infrequent, can be easily dissected manually, focal
3 = frequent, requires sharp dissection, but easily dissected, focal
4 = numerous, requires sharp dissection, moderately difficult to dissect, not focal
5 = numerous, requires sharp dissection, very difficult to dissect, not focal

TABLE 3. **Dissection Plane Grading Scale**

Scale
0 = no adhesions, preservation of dissection plane
1 = thin adhesions, can easily dissect manually, preservation of dissection plane
2 = moderate adhesions, can be dissected, preservation of dissection plane
3 = thick adhesions, can not be dissected, obliteration of dissection plane

postoperative analgesia as required (Burprenorphine). Pigs were housed in individual pens for the survival period of the study. Pigs were humanely euthanized at 4 weeks postoperatively with a lethal dose of sodium pentothal (Lethobarb) administered via an ear vein.

Macroscopic Grading of Adhesion Formation

The costal cartilages and soft tissue attachments of the sternum were sectioned around its perimeter and the sternum and thoracic contents were lifted from the thorax en masse following sacrifice. Careful dissection was performed to allow assessment of the retrosternal and intrapericardial adhesions.

The regions of the heart graded for adhesions included the posterior surface, right and left lateral surfaces, the superior aspect of the anterior surface (where pericardium and sternum were not incised), as well as the inferior aspect of the anterior surface of the heart (exposed to the operative site). A graded scale ranging from zero to five (0 to 5) was used in the grading process as explained in Table 2.

The ability to delineate an anatomical dissection plane between the anterior surface of the heart and the inferior portion of the sternum in the region where the surgery was performed was also assessed and graded using a graded scale ranging from zero to three (0 to 3). The scale used is described in Table 3. The total area of the retrosternal adhesions (as a percentage of the operative site) was also estimated for each animal.

The retrosternal and intrapericardial adhesions were graded for each animal by four observers, who were not aware of the treatment group. However, at the four week survival time, it was possible to discern the resorbable film at the operative site which was evaluated last. Additional observations included the appearance of the pericardium (transparent, translucent, or opaque), and the visibility of coronary vessels, and the macroscopic tissue response to the presence of the film.

Data analysis included descriptive statistics, as appropriate. The categorical data from the pericardial adhesion and dissection plane scores was analysed using Chi Square test.

Histology

The heart and sternum were fixed in phosphate buffered formalin for a minimum of 72 hours. Samples were taken from the posterior, lateral, and anterior aspect of the heart and embedded in paraffin. The sternum was decalcified in formic acid–formalin solution and also embedded in paraffin. Microtome sections (5 microns thick) were cut and were stained with Haematoxylin and Eosin and evaluated under light microscopy using an Olympus microscope as shown in Figure 2. The presence of adhesions and response to the polymeric film were evaluated.

HISTOLOGY TECHNIQUE

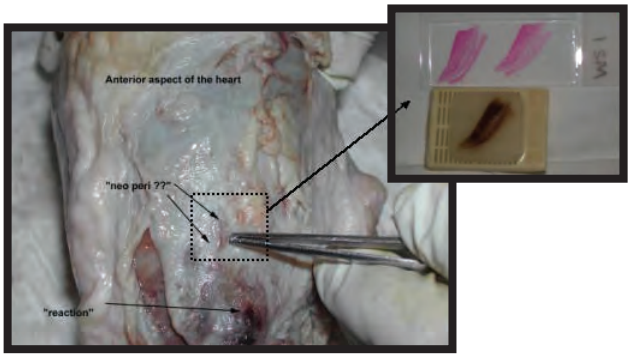

FIGURE 2.
Gross photograph of specimen illustrating the approximate locations of histology samples and cut samples en bloc.

RESULTS

Surgery

There were no operative or postoperative complications. Specifically, there was no evidence of wound infection, wound dehiscence, mediastinitis, respiratory, or gastrointestinal complications in any animal. All animals recovered well from the procedure and were standing and drinking within a few hours, and mobilized and eating by the first postoperative day. Postoperative analgesia was not required beyond the first postoperative day. The wound was macroscopically well healed after 4 weeks.

Adhesion Formation

Grading scale data for the macroscopic dissection, ability to identify and enter anatomic planes, and percentage of retrosternal adhesions at the operative site are presented in Table 4, and shown graphically in Figure 3. The graphical representation of the surgical dissection plane results is summarized in Figure 4. Representative images of the gross dissection observations are shown in Figure 5.

Posterior and Lateral Regions of the Heart

All animals demonstrated sparse adhesions in the posterior region of the heart (Region A), even though this region was not entered surgically. The control group demonstrated higher adhesion scores in the posterior region than all of the treatment groups. In the left and right lateral areas (Regions B and C), all treatment groups demonstrated sparse to infrequent adhesions, while the control group demonstrated adhesions that were frequent to numerous. The control group animals consistently demonstrated markedly higher adhesions scores in Regions A-C as compared to the treatment group animals (Table 4 and Figure 3).

Anterior Region of the Heart

Group 1 - Control

In all control animals the retrosternal space was completely obliterated by the presence of adhesions. The area of the heart exposed to the sternum between the cut pericardial edges (Region D) was adherent to the sternum by numerous thick tenacious adhesions that obliterated the space; all animals received scores of 4 or 5 in this region. The cut pericardial edges were intimately adherent to the posterior surface of the sternum and could not be dissected from it (Region E, all scores of 4 or 5). There was no dissection plane identifiable in any animal, and the retrosternal adhesions occupied an average of 91% of the operative site (range 60-100%). The adhesions were so tenacious, that the tissue was not dissectable from the sternum without risk of damaging the myocardial tissue. The coronary vessels were not identifiable, nor accessible in this region of the heart for the Group 1 animals.

Group 2 – 0.02mm Film Inside the Pericardium

Group 2 animals demonstrated thin focal adhesions between the exposed anterior region of the heart and posterior surface of the sternum between the cut pericardial edges (Region D). These adhesions were easily divided with blunt dissection

TABLE 4. **Adhesion Scoring Results**

Groups	Region A Posterior	Region B Lateral-Left	Region C Lateral-Right	Region D Anterior	Region E Sternum	Area % of Surgical Site	Dissection Plane
Control	2.4 (1-5)	2.9 (1-4)	3.0 (1-4)	4.8 (4-5)	5.0 (4-5)	91% (60-100%)	3.0 (2-3)
0.02mm Film Inside Pericardium	1.5 (1-2)	1.6 (1-3)	1.6 (1-3)	1.9 (1-3)	3.8 (2-5)	18% (10-33%)	1.1 (1-2)
0.02mm Film Inside and Outside Pericardium	1.7 (1-4)	1.4 (1-3)	1.4 (1-3)	1.4 (1-3)	2.3 (1-5)	17.5% (10-40%)	1.1 (1-2)
0.05mm Film Inside Pericardium	1.1 (1-2)	1.3 (1-3)	1.3 (1-2)	1.3 (1-3)	2.1 (1-5)	12% (10-25%)	1.0 (All = 1)
0.05mm Film Inside and Outside Pericardium	1.0 (All = 1)	1.1 (1-2)	1.1 (1-2)	1.3 (1-3)	1.4 (1-2)	13% (10-25%)	1.0 (All = 1)

Data shown are the average of all scores (range). Averages shown are from 20 scores each (5 animals in each group x 4 observers).

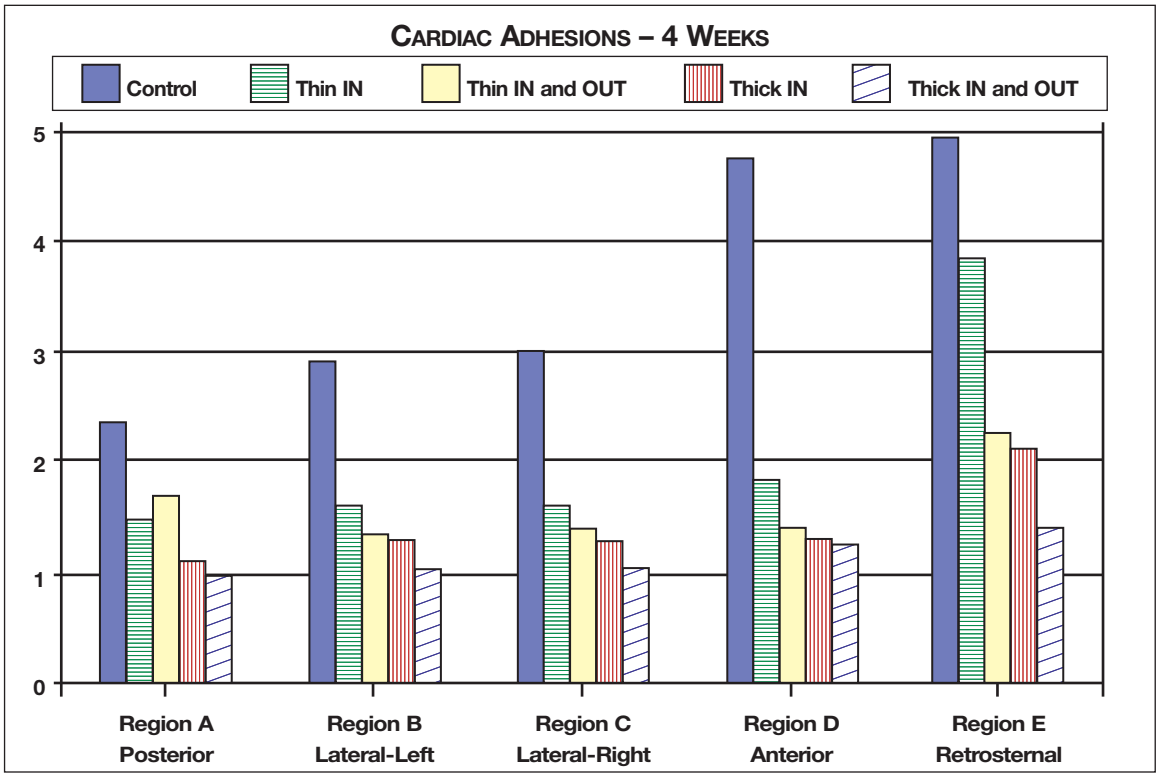

FIGURE 3.
Summary of adhesion scores for the control specimens and the four treatment groups in the various anatomic locations described in Table 2 with the results listed in Table 4.

and all animals received scores of 1 to 3 in this region. The cut edges of pericardium were intimately adherent to the posterior surface of the sternum (Region E, average score 3.8, range 2-5). In contrast to the control animals, a clearly definable anatomic plane was preserved between the exposed region of the heart and posterior surface of the sternum (average score 1.1, range 1-2). The retrosternal adhesions occupied an average of 18% of the operative site (range 10-50%).

In three of the five animals, the defect between the pericardial edges adherent to the sternum was variably filled by the formation of new tissue. This tissue was not dissectable from the sternum. The coronary vessels were easily identifiable and accessible. The 0.02mm film was not visible on macroscopic dissection. There were small remnants of the material present, palpable on the anterior surface of the heart.

Group 3 – 0.02mm Film Inside and Outside the Pericardium

In Group 3 animals, thin focal adhesions were present between the anterior surface of the heart and pericardium (Region D; average score 1.4, range 1-3). The cut pericardial edges were 3 surface of the sternum (Region E; average score 2.3, range 1-5). Similar to the animals in Group 2, the defect between the cut edges of the pericardium showed formation of a new tissue layer that variably closed the defect in 3 of 5 animals. This tissue layer was macroscopically continuous with the cut edges of pericardium and was easily dissectible from the posterior surface of the sternum. Thin focal adhesions were present between anterior surface of the heart and this new tissue layer. A clearly definable anatomic plane was present between the anterior surface of the heart and new tissue layer, as well as between the heart and pericardium. The average dissection plane score was 1.1 (range, 1-2), and the retrosternal adhesions were estimated to occupy and average of 17.5% of the original operative site (range 10-40%). The coronary vessels were easily identifiable and accessible. The 0.02mm thin film was not visible on macroscopic dissection, and there were small remnants of the material present. The material was

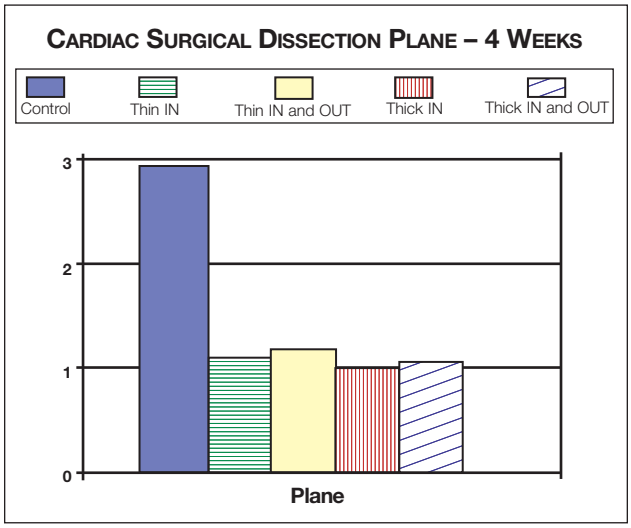

FIGURE 4.
Summary of the surgical dissection plane scores for the control specimens and the four treatment groups described in Table 3 with the results summarized in Table 4.

palpable on the anterior surface of the heart as well as posterior surface of the sternum.

Group 4 – 0.05mm Film Inside the Pericardium

Animals in Group 4 demonstrated thin focal adhesions between the exposed anterior region of the heart and posterior surface of the sternum between the cut pericardial edges (Region D), similar to that observed in Group 2 and Group 3. These adhesions were divided by blunt dissection and the average score was 1.3 (range 1-3). The adhesions between the cut edges of pericardium and the posterior surface of the sternum (Region E) were sparse to infrequent and the majority could be dissected bluntly (average score 2.1, range 1-5). As was observed in Groups 2 and 3, a clearly definable anatomic plane was present between the exposed region of heart and posterior surface of the sternum (all scores 1). The retrosternal adhesions occupied an average of 12% of the operative site (range 10-25%).

In all five animals the defect between the pericardial edges adherent to the sternum was variably filled by the formation of a new tissue layer, greater in magnitude than that observed in Group 2 and Group 3. The coronary vessels were easily identifiable and accessible, as observed in Group 2 and Group 3. The 0.05mm film was visible on macroscopic dissection, and material was palpable on the anterior surface of the heart.

Group 5 – 0.05mm Film Inside and Outside the Pericardium

In Group 5 animals, all adhesions present between the anterior surface of the heart and pericardium (Region D) were sparse and thin, and the average score was 1.3 (range, 1-3). The cut pericardial edges were adherent to the sternum, but focal adhesions were infrequent and could be dissected from the posterior surface of the sternum (Region E; average score 1.4, range 1-2). A clearly defined anatomic plane again was present between the exposed region of heart and posterior surface of the sternum, which was more evident than in each of the other film treatment groups. All animals had a dissection plane score of 1. The retrosternal adhesions were estimated to occupy an average of 13% of the original operative site (range 10-25%).

As was observed in Groups 4, in all animals the defect between the cut edges of the pericardium showed formation of a new tissue layer that variably closed the defect. In contrast to the other groups, however, newly developed tissue was observed on both the interior and exterior surfaces of the film placed outside of the pericardium. This newly developed tissue, or perhaps "neopericardium," is being investigated as a possible pericardial substitute.

The coronary vessels again were easily identifiable and accessible, as observed in all film treatment groups. The 0.05mm film was visible on macroscopic dissection, and material was palpable on the anterior surface of the heart.

Histology

Histologic sections were removed from various regions of the heart, concentrating on the anterior surface as illustrated in Figure 2. Particular attention was directed to the site of original surgery to the pericardium. Histologic sections from control animals demonstrated obliteration of the space normally observed between the layer of pericardium and the epicardium of the heart. Adhesions were observed in histologic sections from all regions, and were consistent with the macroscopic scoring observations. Adhesions were most developed in sections taken from the anterior surface of the heart (operative site) as illustrated in Figure 6.

Sections from the film treatment groups demonstrated adhesions in the posterior and lateral regions, as were observed during dissection. Less frequent and less developed adhesions were observed in sections from the regions where the film was placed.

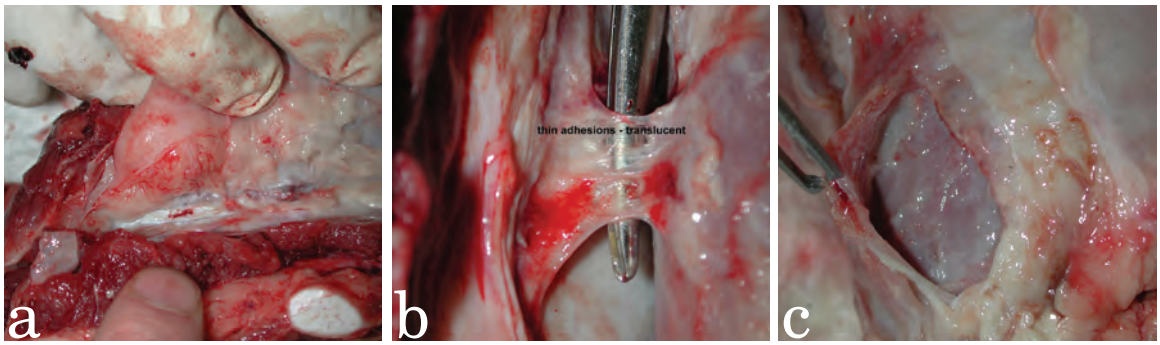

FIGURE 5.
(a) Gross photograph of Group 1 Control specimen – the adhesions were thick and tenacious and the score was 3; (b) gross photograph of Group 3 (0.02 IN + OUT) specimen – there were fewer adhesions immediately adjacent to the film with the general area having grades of 1 to 2. Moderate adhesions were noted around the periphery of the film as opposed to the severe adhesions noted throughout the specimens in the control group; (c) gross photograph of Group 4 (0.05 IN) specimen – the heart was deliverable from the sternum and had a grade of 1. A surgical dissection plane was evident between the repaired pericardium and the heart surface. The vessels were easy to visualize and define.

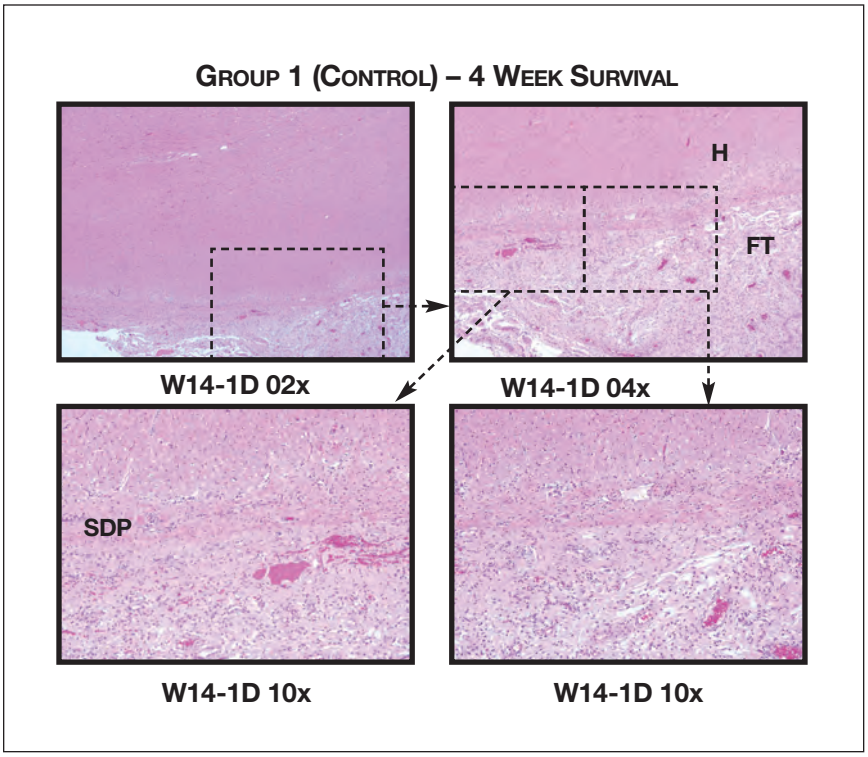

FIGURE 6.
Histology of specimen W14 (4 week survival Group 1: Control). Sections are oriented such that the heart tissue [H] is towards the top and the adhesions are towards the bottom. Dense fibrous tissue [FT] is observed and the heart was firmly adherent to the sternum. There is no surgical dissection plane [SDP] as it is very difficult to discern the difference between the heart and the adherent fibrous tissue.

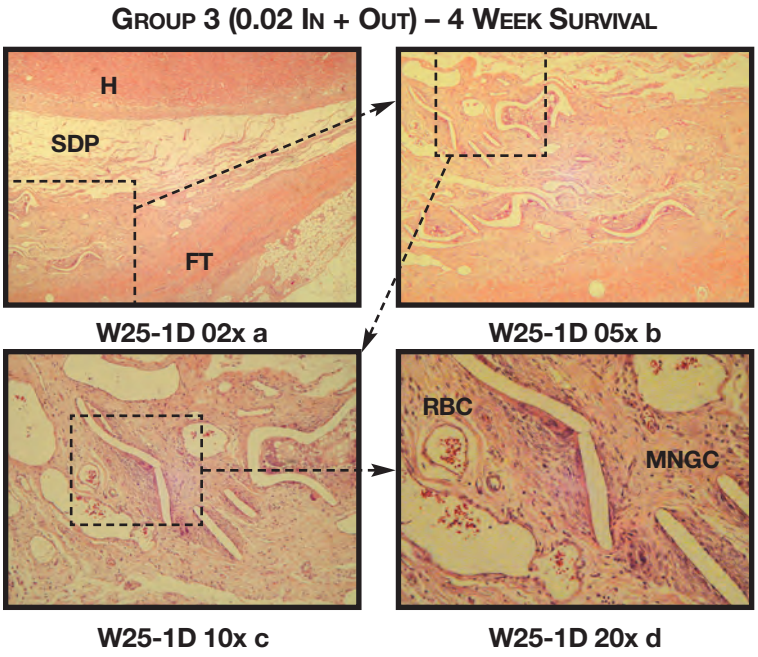

FIGURE 7.
Histology of specimen W25 (4 week survival Group 3: bioresorbable PLA 0.02 IN+OUT). Again, sections are oriented such that the heart tissue [H] is towards the top and the surgical dissection plane [SDP] towards the bottom of the image. Fibrous tissue is observed around the film material helping to create the surgical dissection plane. (a) Histology section with magnification of 2x. Boxes illustrate location of higher magnification views. (b) Histology section with magnification of 5x. (c) Histology section with magnification of 10x. (d) Higher magnification image of multi-nucleated giant cell (MNGC) adjacent to film. Collection of red blood cells [RBC] at a magnification of 20x.

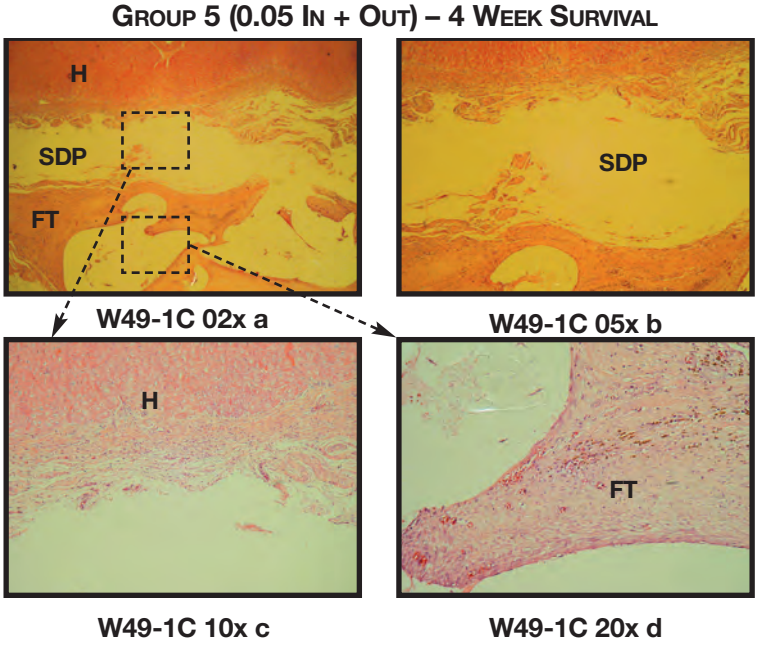

FIGURE 8.
Histology of specimen W49 (4 week survival Group 5: bioresorbable PLA 0.05 IN+OUT). (a) Clear surgical dissection plane [SDP] with fibrous tissue encapsulating the 0.05mm film. (b) Higher magnification view illustrating SDP. (c) Higher magnification of heart surface at 10x. (d) Fibrous tissue encapsulating the 0.05mm film at 20x.

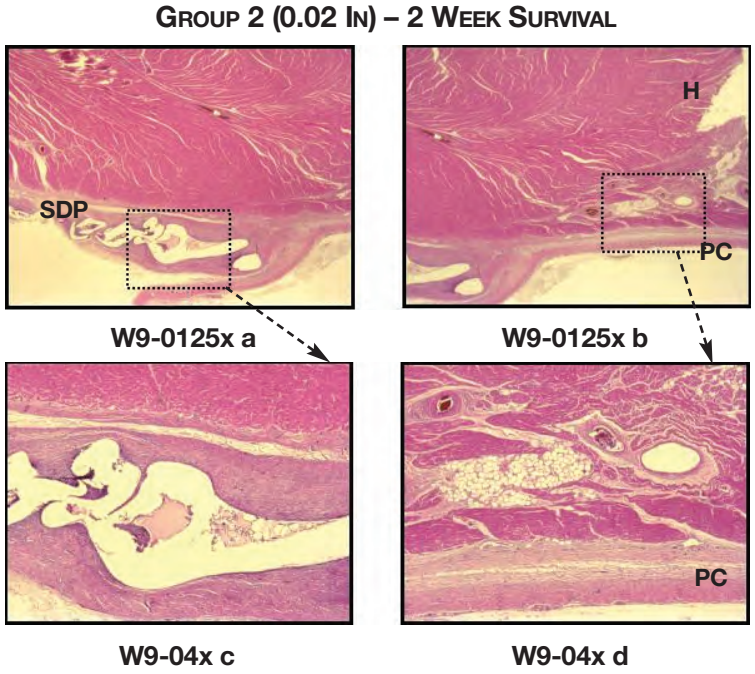

FIGURE 9.
Histology of specimen W9 (2 week survival Group 1: bioresorbable PLA IN). Sections are oriented such that the heart tissue [H] is towards the top and the surgical dissection plane [SDP] towards the bottom of the image. Fibrous tissue is observed around the film material helping to create the surgical dissection plane. The transition to the native pericardium is on the right [PC] (a) and (b) Adjacent histology images with magnification of 1.25x. Boxes illustrate location of higher magnification views. (c) Higher magnification view of the fibrous tissue around the film: 2x. (d) Higher magnification view of the transition to the native pericardium: 4x.

Preservation of a clear space between the pericardium layer and epicardium was seen in all sections from these anterior regions.

In general, a quiescent fibrous tissue layer was observed surrounding the film in all specimens helping to create a clearly identifiable surgical dissection plane. The film was observed in sections from the anterior regions of the heart as illustrated in Figures 7 through 9. The sections are oriented such that the heart tissue [H] is towards the top and the surgical dissection plane [SDP] towards the bottom of the image. Boxes illustrate location of higher magnification views. Fibrous tissue is observed around the film material helping to create the surgical dissection plane. The film was birefringent under polarized illumination. The histologic appearance was typical of a very mild inflammatory healing response to a biocompatible material. There was a mild proliferation of lymphocytes and some multinucleated giant cells and no presence of infection.

DISCUSSION

Intraoperative handling of the film: the surgical team commented that the film was very easy to manipulate and position into the appropriate anatomic location. When placed beneath the pericardium, it was possible to slide the film and reposition it with ease.

Upon gross examination of areas in the vicinity of film placement, localized redness was observed at 2 weeks, returning to normal, without redness at 4 weeks. Histology of these areas revealed a collection small vessels and red blood cells. There was no proliferation or increase in any other cell types, particularly inflammatory cells, suggesting a localized minor abrasion.

In general, a quiescent fibrous tissue layer was observed surrounding the film in all specimens helping to create a clearly identifiable surgical dissection plane. The histologic appearance was typical of a very mild inflammatory healing respone to a biocompatible material with no chronic inflammatory response.

The new tissue layer that was observed macroscopically in the original pericardial window and con-

firmed with histologic examination revealed a fibrous layer similar to the native pericardium. The new tissue layer was more developed and thicker in sections associated with the 0.05mm film, and in sections from Groups 4 and 5.

SUMMARY

- There was a significant difference in the graded adhesion scores between the CONTROL specimens (no treatment) and all the graded adhesion scores anteriorly from animals treated with bioresorbable PLA film (Groups 2 through 5).

- The observations were very consistent within each group indicating that the model is repeatable and a good clinical model.

- All animals returned to normal behavior and did not demonstrate any obvious effects from the placement of the bioresorbable PLA material adjacent to the heart throughout their scheduled survival times of 4 weeks.

- A clear dissection plane was observed in gross dissection and there were notably less adhesions with the bioresorbable PLA film treated groups compared with the CONTROLS.

- Histologic evaluation confirmed a surgical dissection plane observed during gross dissection.

- Histologic evaluation demonstrated a normal biologic response to the film consistent with other biocompatible implant materials.

REFERENCES

Bailey LL, Ze-jian L, Schulz E, Roost H and Yahiku P: A cause of right ventricular dysfunction after cardiac operations: *J Thorac Cardiovasc Surg* **87** (4): 539-42, 1984

Boris WJ, Gu J and McGrath LB: Effectiveness of fibrin glue in the reduction of postoperative intrapericardial adhesions: *J Invest Surg* **9** (4): 327-33, 1996

Bunton RW, Xabregas AA and Miller AP: Pericardial closure after cardiac operations. An animal study to assess currently available materials with particular reference to their suitability for use after coronary artery bypass grafting: *J Thorac Cardiovasc Surg* **100** (1): 99-107, 1990

Dobell AR, and Jain AK: Catastrophic hemorrhage during redo sternotomy: *Ann Thoracic Surg* **37** (4): 273-8, 1984

Duncan DA, Yaacobi Y, Goldberg EP, Mines M, O'Brien D, Congdon F and Carmichael MJ: Prevention of postoperative pericardial adhesions with hydrophilic polymer solutions: *J Surg Res* **45** (1): 44-9, 1988

Duvernoy O, Malm T, Ramstrom J and Bowald S: A biodegradable patch used as a pericardial substitute after cardiac surgery: 6- and 24-month evaluation with CT: *Thorac Cardiovasc Surg* **43** (5): 271-4, 1995

Hendrikx M, Mees U, Hill AC, Egbert B, Coker GT and Estridge TD: Evaluation of a novel synthetic sealant for inhibition of cardiac adhesions and clinical experience in cardiac surgery procedures: *Heart Surg Forum* **4** (3): 204-9; discussion 210, 2001

Hioki M, Iedokoro Y, Yamagishi S, Yamashita Y, Orii K, Hirano S, Hirata T, Masuda S, Kutukata N, Hisayoshi T and Tanaka S: Prevention of postoperative pericardial adhesions with a defibrinogenating agent: *Int Surg* **83** (1): 11-4, 1998

Joyce DH, Cichon R, Muralidharan S, Gu J and McGrath LB: Alteration in pericardial adhesion formation following pretreatment with fibrin glue: *J Appl Biomater* **2** (4): 269-71, 1991

Krause TJ, Zazanis G, Malatesta P and Solina A: Prevention of pericardial adhesions with N-O carboxymethylchitosan in the rabbit model: *J Invest Surg* **14** (2): 93-7, 2001

Loop FD: Catastrophic hemorhage during sternal reentry: *Ann Thorac Surg* **37** (4): 271-2, 1984

Malm T, Bowald S, Bylock A and Busch C: Prevention of post-operative pericardial adhesions by closure of the pericardium with absorbable polymer patches. An experimental study: *J Thorac Cardiovasc Surg* **104** (3): 600-7, 1992

Moro H, Hayashi J, Ohzeki H, Nakayama T, Namura O, Hanzawa K and Yagi N: The effect of fibrin glue on inhibition of pericardial adhesions: *Jpn J Thorac Cardiovasc Surg* **47** (2): 79-84, 1999

Okuyama N, Rodgers KE, Wang CY, Girgis W, Oz M, St Amand K, Pines E, DeCherney AH, Rose EA, Cohn D and diZerega GS: Prevention of retrosternal adhesion formation in a rabbit model using bioresorbable films of polyethylene glycol and polylactic acid: *J Surg Res* **78** (2): 118-22, 1998

Okuyama N, Wang CY, Rose EA, Rodgers KE, Pines E, diZerega GS and Oz MC: Reduction of retrosternal and pericardial adhesions with rapidly resorbable polymer films: *Ann Thorac Surg* **68** (3): 913-8, 1999

Pacholewicz JK, Daloisio C, Shawarby OA, Dharan SM, Gu J and McGrath LB: Efficacy of autologous peritoneum as a biological membrane in cardiac surgery: *Eur J Cardiothorac Surg* **8** (10): 563-5, 1994

Robison RJ, Brown JW, Deschner WP, Highes B and King H: Prevention of pericardial adhesions with dextran 70: *Ann Thorac Surg* **37** (6): 488-90, 1984

Seeger JM, Kaelin LD, Staples EM, Yaacobi Y, Bailey JC, Normann S, Burns JW and Goldberg EP: Prevention of post-operative pericardial adhesions using tissue-protective solutions: *J Surg Res* **68** (1): 63-6, 1997

Wiseman DM, Kamp L, Linsky CB, Jochen RF, Pang RH and Scholz PM: Fibrinolytic drugs prevent pericardial adhesions in the rabbit: *J Surg Res* **53** (4): 362-8, 1992

Manufactured and Distributed By: MAST Biosurgery • 6749 Top Gun Street, Suite 108, San Diego, CA 92121
Toll Free (866) MASTBIO • Fax (858) 550-8060 • Website www.mastbio.com

INTL 105