# Postsurgical Intrapericardial Adhesions: Mechanisms of Formation and Prevention

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**Postsurgical intrapericardial adhesions are still considered an unavoidable consequence of cardiothoracic operations. They increase the technical difficulty and the risk of reoperations. The pathogenesis of postsurgical adhesions is a multistep process, and the main key players are (1) loss of mesothelial cells, (2) accumulation of fibrin in areas devoid of mesothelial cells, (3) loss of normal pericardial fibrinolysis, and (4) local inflammation. Today, very promising methods to reduce adhesions are available for clinical use. This report reviews the process of formation of adhesions and the methods to prevent them, classified according to the mechanism of action.**

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The opening of the pericardial cavity during cardiothoracic operations promotes the formation of postoperative intrapericardial adhesions. This phenomenon is still considered an unavoidable consequence of the operation. More important, intrapericardial adhesions may complicate the technical aspects of reoperations, very often requiring a time-consuming and painstaking dissection to perform the procedure. They increase the risk of inadvertent injury to the heart and great vessels as well as perioperative bleeding. In two large series of cardiac reoperations, the rate of inadvertent injury ranged from 7% to 9% [1, 2]. Bypass grafts and heart chambers were the structures more prone to injury. Surgical dissection of intrapericardial adhesions was the most dangerous period, followed by the resternotomy. Inadvertent injury was associated with poorer outcomes [1, 2] and higher hospital costs [1].

The clinical effect of such risks is amplified by the frequency of reoperations in routine surgical practice. During 2002 to 2006, 6.9% of the isolated coronary artery bypass grafting procedures reported in The Society of Thoracic Surgeons Database were reoperations, accounting for 54,191 of 774,811 procedures [3]. Sabik and colleagues [4] observed an incidence of coronary reoperation of 7% at 10 years and 28% at 20 years after coronary artery bypass grafting. Reoperations occur even more frequently in patients affected by congenital heart disease [5], particularly in staged repair of complex malformations. Moreover, there is evidence that intrapericardial adhesions may hamper diastolic filling of the left ventricle [6].

During the last decades, several methods to prevent the formation of postsurgical adhesions have been proposed but did not gain widespread diffusion in clinical practice. More recently, very promising evidence [7–12] has emerged with the use of products based on polyethylene glycol and hyaluronic acid to prevent adhesions.

The aim of the present report is to summarize available knowledge about the formation and prevention of postsurgical adhesions.

## Material and Methods

A computerized literature search for relevant articles was conducted using PubMed (www.pubmed.org) from the earliest date to September 2012. The entries into the Boolean equation were "pericardial adhesions," "intrapericardial adhesions," "adhesions" **and** "cardiac surgery," "adhesions" **and** "heart surgery," "pericardial barrier," "pericardial substitute," "pericardium" **and** "barrier," "Coseal," "Seprafilm," "REPEL-CV," "CardioWrap," "Adhibit," "SprayGel," "COVA Card," "CorMatrix," and "ePTFE" **and** ("membrane" **or** "barrier"). All relevant articles were reviewed. A comprehensive analysis of the references of each report was performed to identify further articles of interest.

### *Mechanisms of Formation of Postsurgical Intrapericardial Adhesions*

Knowledge about the mechanism of formation of intrapericardial adhesions is based on clinical and experimental studies. However, clinical findings are limited to the intraoperative period. Experimental evidence comes from animal models of acute bacterial pericarditis and peritoneal adhesions. Therefore, with the exception of the period of the operation, the mechanisms of adhesion formation in humans must be inferred from such experimental studies.

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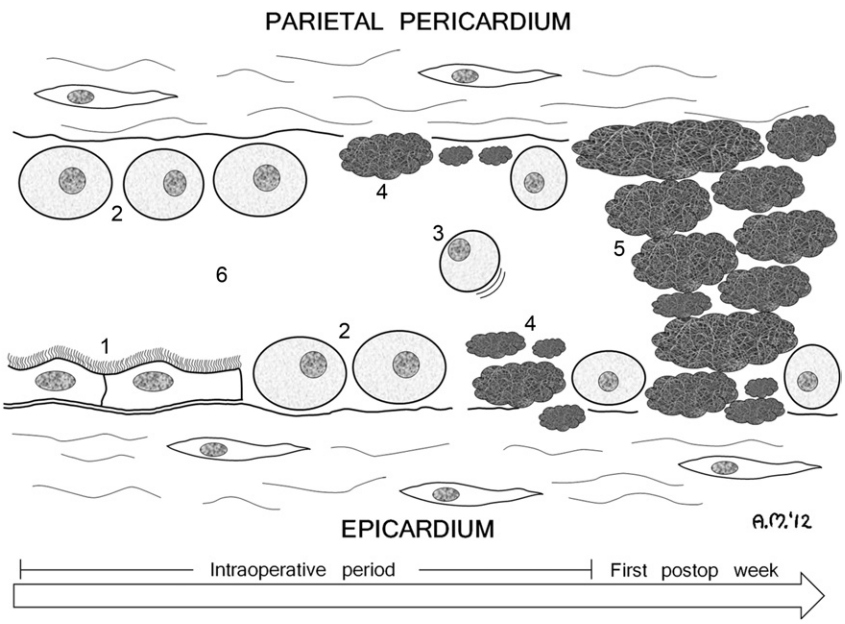


*Fig 1. Diagram shows the early steps for the formation of postsurgical intrapericardial adhesions: 1 = normal pericardial mesothelial cells, tightly adherent to the adjacent cells and the basal lamina, with a flattened shape and covered by microvilli on the luminal surface; 2 = rounded pericardial mesothelial cells, separated from the adjacent cells and the basal lamina, devoid of microvilli; 3 = rounded mesothelial cell free-floating into the pericardial cavity; 4 = fibrin accumulations along the areas devoid of both mesothelial cells and basal lamina with exposure of the submesothelial connective tissue; 5 = bundles of fibrin that fuse denuded areas of visceral and parietal pericardium; 6 = pericardial cavity.*

INTRAOPERATIVE PHASE. Very early morphologic changes of the pericardial mesothelial cells (PMCs) can be observed just after pericardiotomy [13]. PMCs lose their normal flattened shape, appearing rounded and separated from adjacent cells and the basal lamina (Fig 1) [13, 14]. Electron microscopy shows the loss of microvilli that normally cover the PMC luminal surface [13–15]. Early signs of local inflammation (vascular congestion, tissue edema, and white blood cell margination) can be observed. At 135 minutes after pericardiotomy, mesothelial cells detach from the basal lamina and become free-floating into the pericardial cavity, with exposure of submesothelial connective tissue (Fig 1) [13]. The fate of the detached PMCs remains still unknown. Similar pathologic changes have also been observed in an animal model of acute pericarditis by Leak and colleagues [14] within 24 hours after an intrapericardial injection of heat-killed staphylococci.

Denudation of the PMC lining is a key factor for the subsequent formation of adhesions, because fibrin, platelets, and inflammatory cells adhere to denuded areas, creating a scaffold for the connective tissue. Fibrin accumulation is also promoted by a significant decrease of normal fibrinolytic activity of the PMCs, which is evident at 75 minutes after pericardiotomy [13]. Surgical maneuvers on the pericardium are the causes of intraoperative pathologic changes of PMC, including incision, diathermy, retraction, compression beneath sternal retractor blades, desiccation, wetting, local hypothermia, and direct trauma from instruments [13, 16].

EARLY POSTOPERATIVE PHASE (POSTOPERATIVE DAYS 1 TO 7). The early postoperative phase is characterized by large focal accumulation of fibrin conjoining the visceral and parietal surfaces of pericardium devoid of mesothelial lining [14] (Fig 1). Also present on the pericardial surfaces are a large number of inflammatory cells and fibroblasts. Fibrinolysis could be evident in areas with preserved mesothelium.

INTERMEDIATE POSTOPERATIVE PHASE (POSTOPERATIVE DAYS 8 TO 30). A layer of neoconnective tissue is formed on the pericardial surfaces covered by fibrin accumulations and inflammatory cells and fibroblasts [14]. Fibrin strands are the scaffolds for the growth of connective tissue that generates adhesions. Collagen fibers are deposed between the denuded pericardial surfaces and areas of inflammatory cell accumulation. Finally, the connective tissue promotes the fusion between the visceral and parietal pericardium. Early signs of angiogenesis are evident. In clinical practice, very dense and bleeding adhesions can be observed at reoperation during this period.

LATE POSTOPERATIVE PHASE (LATER THAN POSTOPERATIVE DAY 30). The late postoperative period is characterized by the persistence of connective tissue into the areas of pericardial fusion [14]. Moreover, a progressive decrease in the number of blood vessel into the adhesions occurs. On the nonfused surfaces, pericardium is covered by normal PMCs.

REGENERATION OF PERICARDIAL MESOTHELIUM. Two different populations of mesothelial cells could sustain serosal regeneration: free-floating cells and cells surrounding the areas of injury. Early experimental studies on peritoneal mesothelial injury suggested that free-floating precursor mononuclear cells could be involved in the regeneration of the mesothelial layer [17]. These cells adhered to damaged mesothelial surfaces by 24 hours after the injury and formed a defined mesothelial layer by 4 days. More recently, an increase in the number of free-floating mesothelial cells in peritoneal fluid was observed after serosal injury [18]. In an in vivo study on rat testes, Foley-Comer and colleagues [19] used fluorescence labeling to demonstrate that cultured and lavage-derived mesothelial cells adhered to injured serosal surfaces, proliferating and incorporating into the regenerating

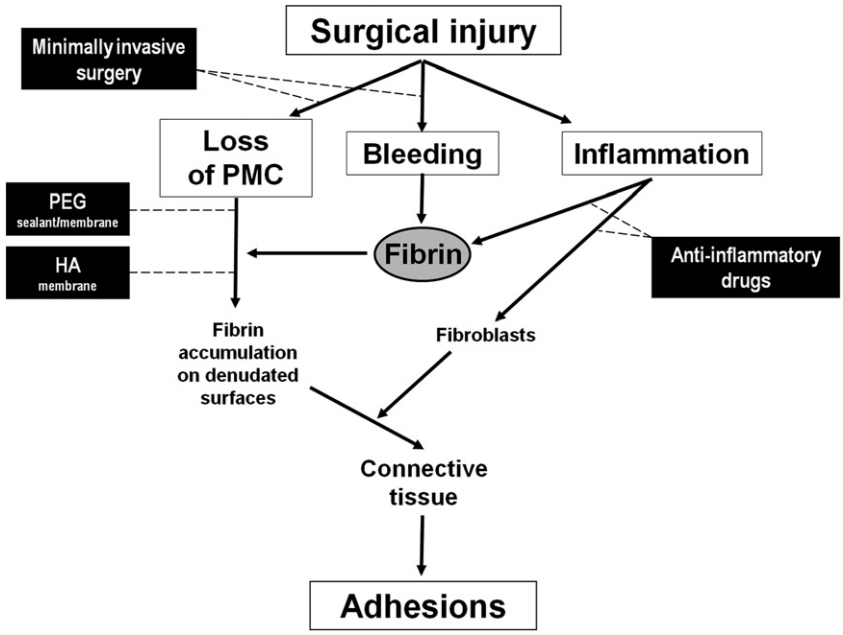


*Fig 2. Chart shows pathogenesis of postsurgical intrapericardial adhesions. Methods to prevent the formation of adhesions are reported within black boxes, and the dotted lines show their level of action within the pathogenetic mechanism. (HA = hyaluronic acid; PEG = polyethylene glycol; PMC = pericardial mesothelial cells.)*

mesothelium. Two origins for such cells have been proposed: mesothelial cells adjacent to the wound and exfoliating after activation, and a preexisting reserve of free-floating mesothelial cells [20]. Early centripetal migration and proliferation of mesothelial cells from the edge of the injured area has been also demonstrated [18, 20]. Mitogens secreted by macrophages that collected around the site of tissue damage were shown to induce mesothelial proliferation [21]. However, experimental evidence about the mechanism of mesothelial regeneration of the pericardium is still lacking, and the hypotheses remain speculative.

PMC regeneration promotes the restoration of normal fibrinolytic activity of the pericardial surfaces. Unfortunately, the timing of regeneration is still unknown in humans, and therefore, it is impossible to infer its effect on the recovery of intrapericardial fibrinolysis. Finally, evidence has emerged showing persistent activation of intravascular fibrinolysis for at least 2 months after cardiac operations [22]. Nevertheless, activation of fibrinolysis was paralleled by a consistent and persistent prothrombotic state. To date, conclusions cannot be drawn about the potential effects of systemic intravascular fibrinolysis on the formation of adhesions into the pericardial cavity during the postoperative period.

### *Methods to Prevent Postsurgical Adhesions*

From previous discussion, four key factors emerged for the formation of postsurgical intrapericardial adhesions: (1) the loss of PMCs with exposure of the submesothelial connective tissue; (2) adhesion of fibrin to the denuded pericardial surfaces; (3) the decrease of normal fibrinolytic activity of pericardial mesothelium; and (4) local inflammation. Here we describe methods to prevent postsurgical adhesions according to the mechanism of action (Fig 2 and Table 1).

### *Prevention of PMC Loss*

MINIMALLY INVASIVE OPERATIONS. Some amount of surgical manipulation of the pericardium is unavoidable in cardiac operations. Nevertheless, this could be kept at a minimum by means of minimally invasive techniques. Ministernotomy and minithoracotomy preserve the integrity of the anterior part of lower pericardium, preventing the formation of direct adhesions between the sternum and the right ventricle. However, objective evidence of a decrease in intrapericardial adhesions after minimally invasive operations is not available to date.

### *Prevention of Fibrin Adhesion to the Pericardial Surface*

DRAINAGE OF SHED BLOOD AND CLOTS. Blood and clots promote the formation of adhesions by means of fibrin accumulation. Careful hemostasis and cavity drainage remain mandatory as universally adopted surgical principles. It is likely that maintaining the pericardial cavity bloodless and free from clots may prevent dense adhesions. Minimally invasive cardiac operations are associated with less postoperative bleeding compared with standard sternotomy [23] and could prevent, to some degree, postsurgical adhesions. Nevertheless, evidence about the relationships among perioperative bleeding, retained hematoma, numbers and positions of chest tubes, and the severity of postsurgical adhesions is still lacking.

POLYETHYLENE GLYCOL SEALANT. Coseal (Baxter Healthcare, Fremont, CA) is a surgical sealant composed of two synthetic polyethylene glycols that was approved by the U.S. Food and Drug Administration as a vascular anastomotic sealant in 2001. Coseal is provided in kits of 2, 4, and 8 mL. The two glycol solutions polymerize after mixing to form a hydrogel that can be sprayed in a thin layer over the epicardium. The product then swells up to

*Table 1. Currently Available Products to Prevent Postoperative Intrapericardial Adhesions*

| Product Name [ref] | Manufacturer | Mechanism of Action | Resorbable | FDA Approval or Clearance | CE Mark |
|---|---|---|---|---|---|
| CardioWrap [30] | MAST Biosurgery (San Diego, CA) | Polylactic acid sheet<br>Prevention of fibrin adhesion | Yes | Yes | Yes |
| CorMatrix [37] | CorMatrix Cardiovascular (Atlanta, GA) | Extracellular matrix membrane<br>Prevention of fibrin adhesion | Yes | Yes | Yes |
| Coseal [7–10, 24] | Baxter Healthcare (Fremont, CA) | Sprayable polyethylene glycol<br>Prevention of fibrin adhesion | Yes | Yes | Yes |
| Cova CARD [38, 39] | Biom'Up (Lyon, France) | Porcine collagen membrane<br>Prevention of fibrin adhesion | Yes | N/A | Yes |
| REPEL-CV [12, 28, 29] | SyntheMed (Iselin, NJ) | Polylactic/polyethylene glycol membrane<br>Prevention of fibrin adhesion | Yes | Yes | Yes |
| Seprafilm [11, 33–36] | Genzyme (Cambridge, MA) | Hyaluronic acid membrane<br>Prevention of fibrin adhesion | Yes | Yes | Yes |

CE = Conformité Européene; FDA = Food and Drug Administration; N/A = not applicable.

four times its volume, and additional swelling occurs as the gel resorbs [24].

Polymeric sealants such as Coseal have a biologically very sound rationale in terms of the prevention of postsurgical adhesions. In fact, when sprayed over the pericardial surfaces, they cover the areas devoid of mesothelial lining and impede the adherence of fibrin and the fusion between the serosal surfaces (Fig 3). In this way, the sealant prevents the formation of the fibrin scaffold. Moreover, within 30 days after the operation, the polymer is completely reabsorbed, avoiding the potential complications, such as persistent inflammation, fibrosis, and infection, related to permanent foreign bodies.

Several clinical reports are available about the use of Coseal in cardiac surgery, particularly in the field of pediatric patients and after ventricular assist device implantation [7–10]. A multicenter international clinical study reported Coseal was associated with filmy and avascular adhesions in 85% of pediatric cardiac patients at reoperation [8]. However, a control group was absent. Serious adverse events related to Coseal were infrequent. Some events, in particular, occurred in the early part of the study and were probably due to an excessive amount of product that caused cardiac tamponade and occlusion of the superior vena cava when it swelled [8]. The dosage of Coseal was calibrated according to the child's body weight in the later part of the study, and no other complications occurred. That Coseal swelling could also produce such adverse events in adults seems unlikely.

Our group very recently reported the histologic evidence at 1 year from Coseal use after intracorporeal left ventricular assist device (LVAD) implantation [10]. At necropsy, we observed very scanty and filmy avascular adhesions on the anterior aspect of the left ventricle that

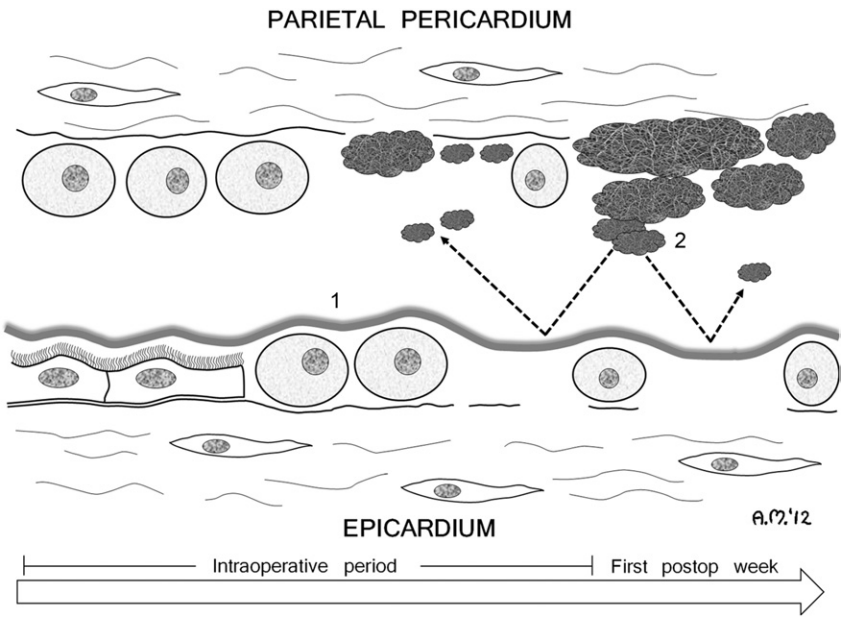


*Fig 3. Diagram shows the mechanism of action of sealants and resorbable membranes. A layer of product (1) impedes the adherence and accumulation of fibrin on the exposed submesothelial connective tissue along the epicardium (2), preventing the fusion between the visceral and parietal pericardium.*

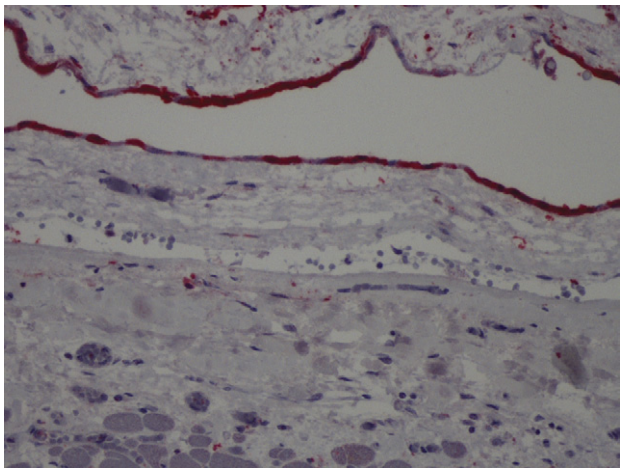

*Fig 4. Calretinin antibody staining in this photomicrograph of a specimen from the anterior wall of the left ventricle, 1 year after treatment with Coseal, shows the integrity of the mesothelial cells along both the layers of the pericardium, without connective tissue between the visceral and parietal pericardium.*

was sprayed with Coseal during the operation. However, on the inferior wall of the left ventricle, not treated with Coseal and serving as the control, denser adhesions were found. Histologic analysis showed no connective tissue between the serosal layers on the treated surface (Fig 4), whereas it filled the pericardial space along the inferior wall of the left ventricle (Fig 5). Moreover, immunohistochemistry analysis confirmed the integrity of the mesothelial cells along the treated surface (Fig 4). Nevertheless, this evidence was limited to only one case, and confirmation in larger studies is needed.

Other similar sealants, based on polyethylene glycol, and reported in literature, are Adhibit (Cohesion Technologies, Palo Alto, CA) [25] and SprayGel (Confluent Surgical Inc, Waltham, MA) [26]. Adhibit was associated with a reduction in adhesions extent and tenacity in a series of pediatric cardiac patients [25], whereas Spraygel did not significantly decrease intrapericardial adhesions after the Norwood I operation [26].

POLYLACTIC ACID AND POLYETHYLENE GLYCOL. The REPEL-CV adhesion barrier (SyntheMed Inc, Iselin, NJ) is a bioresorbable transparent membrane (size, 18- × 13.5-cm; thickness, 5.5 mm) [12]. It is a mixture of polylactic acid (52%) and polyethylene glycol (47%) and is resorbed completely within 28 days. Experimental [27] and clinical evidence [12, 28, 29] showed that REPEL-CV was safe and associated with a reduction of severe postoperative adhesions after cardiac operations. However, severe adhesions were observed in 2 patients after LVAD implantation in 1999 [12]. It has been speculated that mechanical stresses generated by the pulsating outflow graft disrupted the integrity of the adhesion barrier; therefore, REPEL-CV was considered contraindicated in LVAD implantation. Nevertheless, currently available LVAD pumps generate pulseless continuous flow and the contraindication could not be still considered valid.

POLYLACTIC ACID. CardioWrap (MAST Biosurgery, San Diego, CA) is a bioresorbable membrane composed of L-lactide (70%) and D,L-lactide (30%). Sheets of 10 × 13 cm or 13 × 20 cm are available. It is completely resorbed within 6 months from application by hydrolysis. In an animal study, a polylactide sheet limited limit adhesion formation compared with controls [30].

CHITOSAN. Carboxymethyl chitosan is a resorbable biopolymer obtained from chitin after thermal sterilization. From the molecular point of view, it is very similar to hyaluronic acid. It is extracted from the exoskeleton of crustaceans and insects. In a randomized animal study, Daroz and colleagues [31] reported a significant reduction in intensity of postsurgical adhesions and in dissection time after intrapericardial instillation of chitosan compared with controls.

RESORBABLE HYALURONIC ACID MEMBRANE. Seprafilm (Genzyme, Cambridge, MA) is a bioresorbable membrane [11, 32, 33] composed of sodium hyaluronate and carboxymethylcellulose (size, 12 × 12 cm). It is simply applied to the dry mediastinum just before sternal closure and does not require stitches for anchoring. Seprafilm hydrates within 48 hours after application and forms a gel coating, increasing its volume [34]. The hydrophilic gel acts as a barrier to separate pericardial surfaces, preventing the formation of fibrin bundles (Fig 3). Time to resorption from the application site is 7 days [34]. van der Linden and colleagues [33] reported a reduction, albeit nonsignificant, in retrosternal adhesions in patients who underwent coronary artery bypass grafting and received Seprafilm compared with controls. Seprafilm was used in 350 pediatric patients who underwent operations for congenital heart defects, and 30 patients underwent reoperation within a mean of 12 months after the first procedure [11]. The authors observed a 10% reduction in the extent and tenacity of intrapericardial adhesions compared with 10 random control patients and according to a subjective

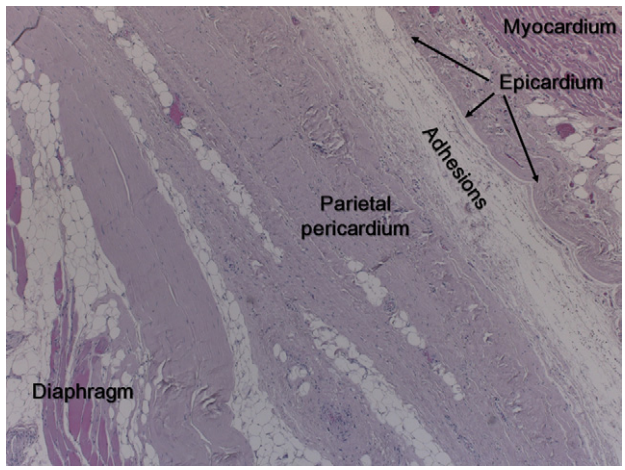


*Fig 5. Photomicrograph shows a specimen from the inferior wall of the left ventricle, 1 year after operation and not treated with sealant. The space between the pericardial layers is filled by loose connective tissue of the adhesions. Hematoxylin and eosin stain.*

adhesion scoring. A significant reduction of dissection time was reported in patients treated with Seprafilm. Notably, no complications related to the membrane were reported in the study. Seprafilm clinical use was generally recognized as safe [35, 36]. Nevertheless, a significantly higher incidence of serious adverse events (fistula, abscess, peritonitis, sepsis) secondary to anastomotic intestinal leak has been observed in patients when Seprafilm was wrapped around a fresh anastomotic site compared with controls [35, 36].

EXTRACELLULAR MATRIX MEMBRANE. CorMatrix (CorMatrix Cardiovascular, Atlanta, GA) is a patch made of extracellular matrix and clinically adopted for intracardiac and pericardial repair in operations for congenital heart defects. It acts as a scaffold to promote the migration and proliferation of the patient's own cells to repair tissue. Reoperation after CorMatrix use has been reported in 1 patient to date. The authors observed that the pericardial sac was macroscopically similar to normal pericardium and that adhesions were mostly filmy and avascular beneath the patch [37].

RESORBABLE PORCINE COLLAGEN MEMBRANE. Cova CARD (Biom'Up, Lyon, France) is a bioengineered membrane made of purified porcine tendon type I collagen. In animal studies, the absorption of the membrane occurred within 4 months [38, 39]. Animals treated with Cova CARD had loose intrapericardial adhesions and a lower adhesion score than the controls. No inflammatory reaction was observed, and fibrosis was minimal. The membrane allowed restoration of the mesothelial layer on the pericardial surface. Published reports about clinical use of Cova CARD are still unavailable.

### *Restoring Intrapericardial Fibrinolysis*

The fibrinogens tissue plasminogen activator and streptokinase were reported to be effective in reducing the extent and tenacity of adhesions in a rabbit pericardial adhesion model [40]. However, significant postoperative bruising and bleeding occurred. Because of the risk of bleeding, systemic or topical postoperative use of fibrinolytics is contraindicated after cardiothoracic operations.

### *Control of Inflammation*

Local inflammation, secondary to surgical injury, is a key player in the pathogenesis of postsurgical adhesion. Corticosteroids and nonsteroidal antiinflammatory drugs have been tested in adhesion prevention. Vander Salm and colleagues [41] reported that in a canine model of postsurgical adhesions, intravenous and oral methylprednisolone prevented the formation of any adhesion in most of the animals but that intravenous and oral ibuprofen did not prevent dense adhesions in most cases.

Dexamethasone-loaded biodegradable copolymer films for site-specific drug delivery were examined in a rabbit model of postoperative cardiac adhesions [42]. Treated animals showed a significant reduction of intrapericardial adhesions compared with controls. Site-specific drug delivery could be advantageous because it could minimize the risk of systemic adverse effects of steroidal therapy. However, clinical experience with this route of administration has still not been reported.

Iskesen and colleagues [43] observed a significant decrease in the formation of postoperative intrapericardial adhesions, with preservation of pericardial fibrinolytic properties after the intramuscular injection of piroxicam in a rabbit model. The intramuscular injection of indomethacin was equally effective as Coseal in reducing the extent and density of postsurgical adhesions in piglets [44].

Although experimental evidence is promising, antiinflammatory drugs are still not routinely adopted in clinical practice to prevent adhesions because of the risk of serious adverse effects during the postoperative period such as infection, impaired wound healing, and gastrointestinal bleeding. Antiinflammatory drugs could also have deleterious effects on mesothelial regeneration that is upregulated by inflammatory cells [21].

### *Other Methods*

KERATINOCYTE GROWTH FACTOR. Proliferation of mesothelial cells is stimulated by keratinocyte growth factor (KGF) [45]. It has been hypothesized that upregulating PMC regeneration could reduce adhesions by means of earlier recovery of mesothelial fibrinolytic potential [46]. Recombinant human KGF was tested in an experimental setting to evaluate the effect on the formation of postsurgical pericardial adhesions. Lopes and colleagues [46] observed a significant reduction in the severity of adhesions and in time and maneuvers of dissection after intrapericardial KGF injection use compared with controls. Unfortunately, PMC integrity and serosal fibrinolytic activity have not been evaluated. This group also reported the synergistic effect of the combination of KGF and chitosan [47]. They observed a significant reduction of the adhesion score after the combined use of KGF and chitosan compared with controls and with the use of KGF or chitosan alone. Moreover, the KGF-treated animals showed a more extensive presence of mesothelial cells than controls.

VODKA. Moderate alcohol consumption has been shown to decrease the inflammatory state [48]. The antiinflammatory effect could be explained by the modulation of the level and function of circulating lipoproteins [49]. In fact, hypercholesterolemia is associated with an increase of markers of inflammation and oxidative stress [50]. Moreover, red wine contains resveratrol and flavonoids, such as fisetin and quercetin, which have antioxidant and antiinflammatory properties. In a very recent experimental study, the group of Sellke [51] reported that postoperative vodka consumption markedly reduced the formation of pericardial adhesions, whereas red wine did not show an effect. The authors speculated about such difference:

First, a more intense postoperative inflammatory state and higher levels of low-density lipoprotein cholesterol were observed in the group treated with red wine compared with vodka. This finding could explain why adhesions were more severe in the first group.

Second, they also hypothesized that the mechanism of adhesion reduction could be an effect of ethanol on the posttranslational modification of collagen deposition or cross-linking. Differently from vodka, red wine may contain a compound that inhibits this effect of ethanol. Otherwise, different peak plasma concentrations for ethanol could explain the effects of vodka and red wine on pericardial adhesions. The authors speculated about a potential therapeutic window of ethanol in terms of adhesion prevention. Serum ethanol level was about twofold higher after wine consumption compared with vodka, and it could be outside the therapeutic window of ethanol, explaining the lack of effect of red wine on adhesions.

MELATONIN. Saeidi and colleagues [52] recently reported a marked reduction in the adhesion score in a canine model after the intrapericardial instillation of a mixture of melatonin and ethanol. They suggested that the antioxidant and scavenging properties of melatonin could prevent adhesions.

### *Physical Barriers*

NONRESORBABLE EXPANDED POLYTETRAFLUOROETHYLENE MEMBRANES. Expanded polytetrafluoroethylene (ePTFE) is routinely adopted as a pericardial substitute in cardiac operations [53]. The membrane functions to create a physical barrier separating the heart and the great vessels from the posterior table of the sternum to reduce the risks of inadvertent injury during resternotomy. It has also been adopted to protect the outflow cannula of intracorporeal LVADs [54]. However, ePTFE does not prevent the formation of intrapericardial adhesions. In animal studies, a significantly thicker layer of subepicardial neotissue fibrosis was demonstrated after the application of an ePTFE membrane [32, 55]. In clinical experience, anatomic landmarks on the epicardial surfaces, like as coronary vessels, could become indistinct on the surfaces covered by the membrane because of fibrosis [11, 26, 38]. Even severe constrictive adhesions have been reported after the use of a pericardial ePTFE membrane [56, 57]. Moreover, as with any nonresorbable foreign body, it is prone to a lifelong risk of infection.

A recent experimental study by the group of Backer [55] found the isolated use of ePTFE pericardial membrane was associated with adhesion score and thickness similar to controls. However, if combined with a polymeric film composed of polyethylene glycol and polylactic acid, ePTFE membrane showed a significantly lower adhesion score than ePTFE alone and controls. Naito and colleagues [32] reported similar results. This experimental evidence seems to be very promising and could justify the simultaneous use of ePTFE membrane for anatomic protection during resternotomy and a polymeric film to prevent adhesions. This combination has been already described in LVAD patients [9]. However, in a clinical study by Salminen and colleagues [26], ePTFE impaired epicardial visibility at reoperation and tended to increase the severity of adhesions even when combined with Spraygel, a polyethylene glycol polymeric film. It is noteworthy that in the same study, Spraygel did not decrease significantly adhesions, even in the absence of an ePTFE membrane.

PERICARDIAL CLOSURE. Routine closure of pericardium at the end of the operation could be considered as an autologous physical barrier. As reported by Rao and colleagues [58], routine closure of the pericardium resulted in a larger distance between the posterior table of the sternum and the epicardium but was associated with a decrease of the cardiac index in the early postoperative period. However, it does not prevent the formation of fibrin bundles between serosal surfaces and is usually unfeasible in reoperations because of lack of tissue.

In conclusion, cardiac reoperations represent a significant fraction of routine surgical practice. The risk of inadvertent injury remains not negligible at reoperation, even in high-volume centers. Injury to the heart or bypass grafts is associated with a higher rate of in-hospital death and complications [1, 2]. It is noteworthy that most adverse events occur after resternotomy, namely, during the dissection of adhesions. Therefore, routine adoption of methods to prevent the formation of intrapericardial adhesions could decrease the risks related to reoperations. Among the methods reviewed here, available clinical evidence shows that products based on polyethylene glycol or hyaluronic acid seem to be the most promising to date. They have a biologically very sound rationale: they impede the accumulation of fibrin between pericardial surfaces and are fully reabsorbed within 30 days, without interfering with PMC regeneration. They are also devoid of the risk of the serious systemic adverse effects of antiinflammatory drugs. Nevertheless, because of the potential risk of local side effects, such products must be used carefully and according to manufacturer instructions.

Other materials and methods are still waiting for clinical outcomes. Notably, ePTFE membrane, albeit effective to protect the heart during the resternotomy, induces a strong fibrotic reaction on the epicardium and should be considered a physical barrier rather than a method to prevent adhesions. The combination of ePTFE membrane and polyethylene glycol film could be particularly advantageous in risky cases such as when a conduit is in close contact with the sternum. However, the demonstration of clinical efficacy and cost-effectiveness of such methods is hampered by the low short-term and medium-term rate of reoperation in cardiac surgical patients. Operations for congenital heart disease and LVAD are probably the best-suited fields in which to perform further evaluation of methods to prevent intrapericardial adhesions.

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