PeriGel: A Pericardial Adhesion Barrier

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Introduction

The proliferation of post-operative fibrous pericardial adhesions in patients receiving open-chest surgery is a situation critically in need of medical innovation. Approximately 6-17% of cardiac surgeries will require reoperation because of adhesions between the pericardium and the thoracic wall as well as the myocardium which can inhibit natural cardiac motion[1,2]. Adhesions cause extended operation times and their removal can risk catastrophic damage to the nearby heart and lungs. With more than 200,000 coronary bypass surgeries and over 100,000 other open-chest operations performed per year in the United States alone[1], it quickly becomes apparent how critical it is to develop more effective means of preventing these adhesions and reduce the risk of complications in those receiving open-heart surgeries.

Anatomy

The pericardium is a double-walled fluid-filled sac that surrounds the myocardium (cardiac muscle layer)[3]. It is composed of an external fibrous wall and an internal serous region, which is subdivided into the parietal and visceral regions. The external face of the pericardium is bounded by a mesothelial cell wall providing a slick surface against which the serous pericardial fluid can flow without friction. The arrangement of these layers is depicted in *Figure 1*.

The pericardium serves several crucial roles in the proper sustained functioning of a beating heart. It provides protection from infection to the heart in the form of its fibrous outer wall and fluid barrier, preventing malicious microbial activity in the lungs from spreading to the heart. It provides lubrication to the heart, preventing restrictions to its ability to beat. Additionally, the pericardium serves as a medium for maintaining cardiac positioning and size, preventing the heart from overfilling with blood. This last responsibility is achieved through its physical attachment to the diaphragm.[3]

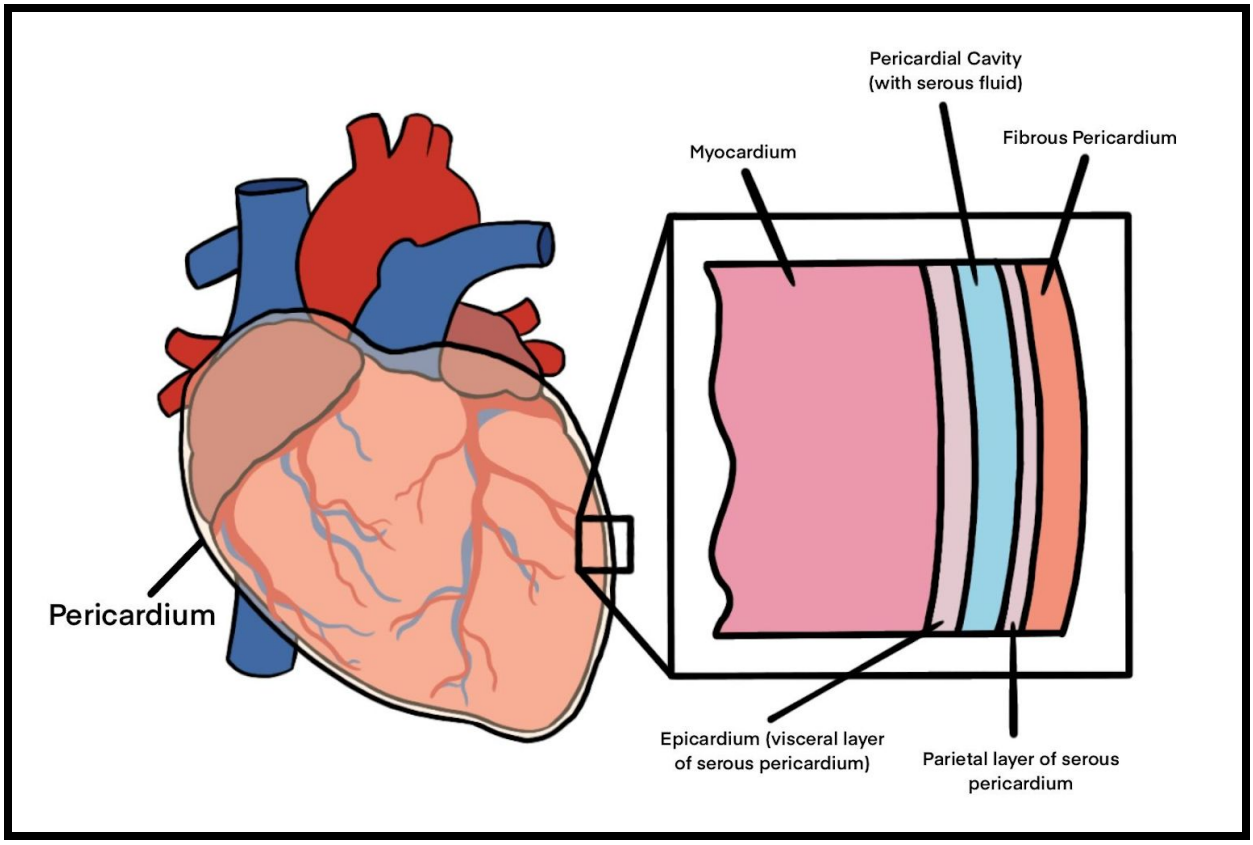

Figure 1. Diagram of layers of the pericardium. The pericardium contains a serous fluid layer within the serous tissue layer that serves as a lubricant and protective layer between the myocardial wall and the rest of the thoracic cavity.

Pathologies of the Pericardium

Numerous pathologies can be observed in the human pericardium. The majority of failure modes stem from inflammatory response. Pericarditis, pericardial effusion, and adhesions all result from the subtly different mechanisms by which inflammation can cause more harm than good[4]. They all result in similar symptoms as the heart becomes pressurized and the pericardium's ability to achieve its function is weakened: shortness of breath and chest pain. Though all forms of inflammatory dysfunction of the pericardium are important to address, the case of adhesions stands out as particularly suitable for an intervention due to their inherently physical manifestation.

Pericardial adhesions form in the case of open-chest cardiac surgery, such as in heart bypass surgery, wherein the pericardial barrier must be broken in the surgical process. Due to the significant trauma to surrounding tissue, adhesions are particularly prevalent and severe in cardiac surgical cases[5]. A diagram of the physical manifestation of the adhesions is shown in *Figure 2*.

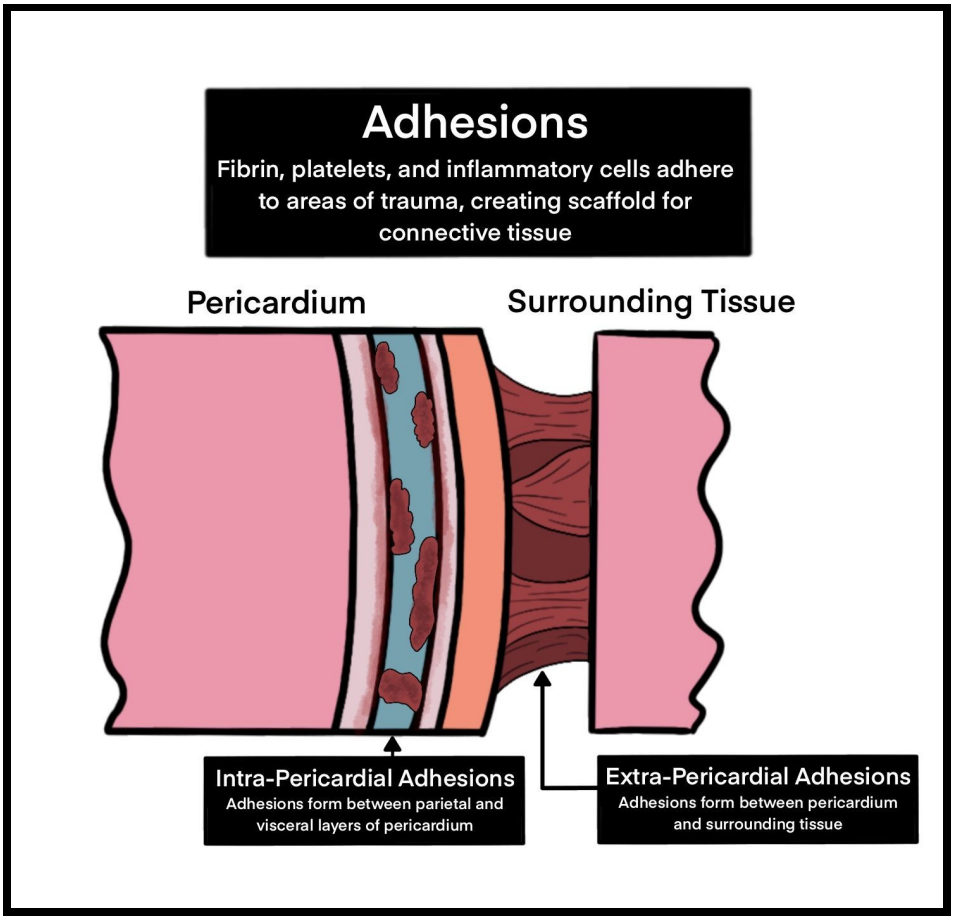

Figure 2. Diagram of internal and external pericardial adhesions. Internal adhesions adhere within the serous fluid region and increase pericardial friction on the myocardial wall, while external adhesions to the thoracic cavity present significant surgical challenges upon reentry.

Upon suturing and the finalization of surgery, the protective surface of the mesothelial cell wall is damaged, causing some of the pericardial mesothelial cells (PMCs) to die and others to float into the serous pericardial fluid region. This exposes inner fibrous connective tissue

within the pericardium to the outside of the organ. Since the circumstance in which it occurs is in surgery, there is a high quantity of blood flowing in the region as well. The loss of PMCs additionally prevents the expression of glycoprotein-4 (PRG4), an inflammatory inhibitor for myofibroblasts. The circumstance of surgical incision additionally activates cyclooxygenase enzyme 2 (COX-2), which enables the production of prostaglandins that signal for increased inflammatory response from the myofibroblasts[6]. The combination of high blood volume, exposed fibrous surfaces, and the natural inflammatory response to injury mediated by COX-2 leads to a significant accumulation of fibrous extrusion[2,5,6] from the pericardial surface. This process continues until it reaches another region of scar tissue: the thoracic cavity wall inside the patient's chest, to which the fibrous extrusion attaches. At that point, an adhesion has been formed. A similar process occurs on the internal face of the pericardium, which forms internal adhesions to the myocardial surface. The pathological progression from surgical injury to adhesion formation is depicted in *Figure 3*.

Currently Available Treatments

Modern treatments of pericardial adhesions are ineffective and often involve products intended for different portions of the body. The three most commonly used treatments are Coseal, Seprafilm, and Interceed. Each of them has its own problems, and even the most effective of these current treatments only reduces severe adhesions by 40%[7].

Some modern treatments, such as Coseal, tend to use a spray-on application method, along with a hydrogel structure that adheres to the pericardial surface to physically constrain the formation of adhesions. However, the hydrogel that Coseal uses is covalently bonded and not capable of dynamic crosslinking, and so it tends to fracture with any motion; it was not intended for use under cyclic loads on the heart, but rather in the abdominal region. It is also prone to swelling (upwards of 400% of its original applied volume), which can unintentionally lead to compression of the heart.[5]

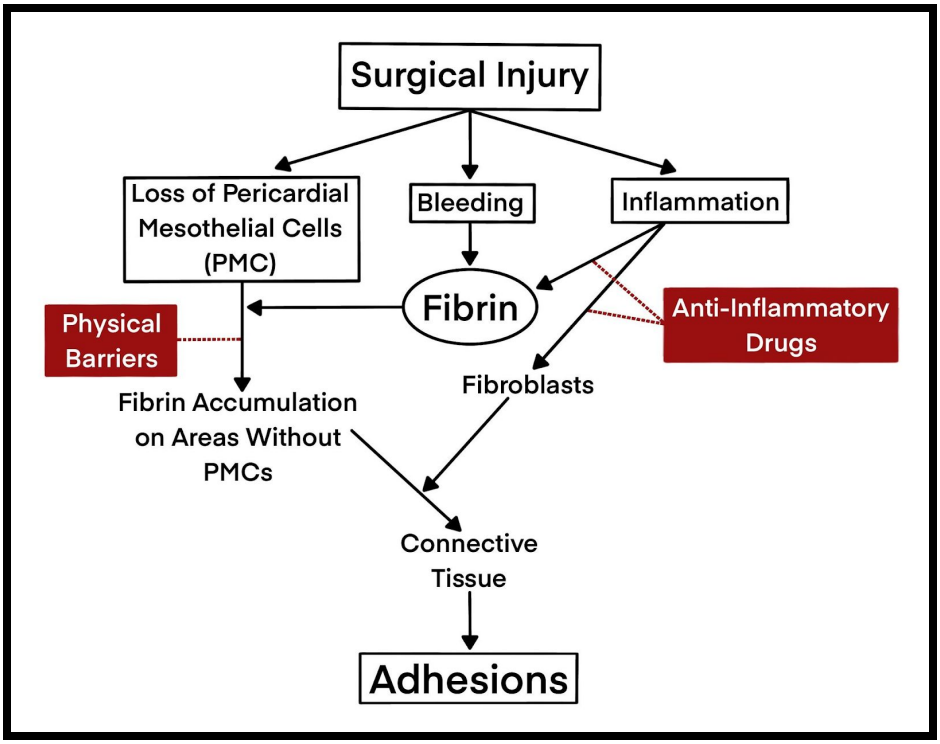

Figure 3. The pathology of adhesion formation with emphasis on potential clinical intervention points. The inflammatory response to injury combines with the presence of blood and the loss of the protective mesothelial cell layer to create optimal conditions for fibrous outgrowth formation.

Other modern treatments stick with a solid resorbable physical membrane in the shape of a sheet. REPEL-CV and Seprafilm[8] (composed of carboxymethylcellulose and hyaluronic acid) both work this way. The failure mode of these solid sheet devices is in their inability to remain in one place as the heart beats and the patient moves around over time. These treatments were designed for use in the abdominal and pelvic region[6], not on a beating heart. Additionally, as sheets of a particular size and shape, they are poorly suited to the dynamic and irregular nature of the pericardial surface.

Both types of modern treatments for pericardial adhesions have minimal to no effect on intrapericardial adhesions, and only modest results for extrapericardial adhesions. One contributory reason for their inefficacy in extrapericardial adhesion prevention is the fact that they largely degrade by the end of the first week of their application[2], whereas the timeline for

major pericardial adhesions is over the first two weeks post-operation[5]. Additionally, modern treatments only target the physical extrusion of the adhesion rather than the biochemical basis for their creation.

Toward a Solution: Introducing PeriGel

A potential avenue for the prevention of pericardial adhesions is to target adhesion formation both physically and biochemically. PeriGel takes this two-pronged approach to dramatically reduce adhesions after cardiac surgeries. The application of PeriGel to the pericardial surface prior to chest closure acts as a physical barrier between the surfaces of the chest wall and the pericardium, while the drug-eluting nanoparticles in PeriGel inhibit the biological activity that directly contributes to the formation of post-operative adhesions both internally and externally.

Components & Materials

PeriGel consists of bioabsorbable drug-eluting nanoparticles suspended within a viscous hydrogel. The hydrogel is composed of dodecyl-modified hydroxypropylmethylcellulose (HPMC-C_{12}) and biodegradable polymeric nanoparticles (NPs) comprising poly(ethylene glycol)-b-poly(lactic acid) (PEG-b-PLA). HPMC-C_{12} is biodegradable and tissue adhesive[9]. PEG-b-PLA core-shell NPs have been previously used as drug delivery vehicles in a wide range of in vivo applications with a diameter of approximately 100 nm[10]. These 100 nm NPs are used in the formation of the final hydrogel by mixing them into an aqueous solution of HPMC and allowing gel formation. The hydrogel physical properties can be altered by adjusting the weight ratios of the polymer and NP. A polymer-to-NP ratio of 1:10 was chosen based on its previous performance as an adhesion barrier in a rat cardiac model[2]. *Figure 4* demonstrates the dynamic cross-linking properties of PeriGel.

The anti-inflammatory being used in PeriGel is indomethacin, a non-steroidal anti-inflammatory (NSAID). Indomethacin largely inhibits the expression of the cyclooxygenase (COX) 1 and 2 enzymes and reduces the production of prostaglandins[11]. Indomethacin also

inhibits monocyte and macrophage accumulation in the area to minimize mesothelial proliferation[12].

PeriGel is capable of viscous flow when under significant shear stress which allows it to be directly sprayed onto the surgical site with compressed air. A spray on application allows for more general coverage and conformation to desired tissue. Due to dynamic cross-linking, PeriGel can rapidly recover from the fluid-like state to a more solid-like state within five seconds after pressurized application to the pericardial surface.

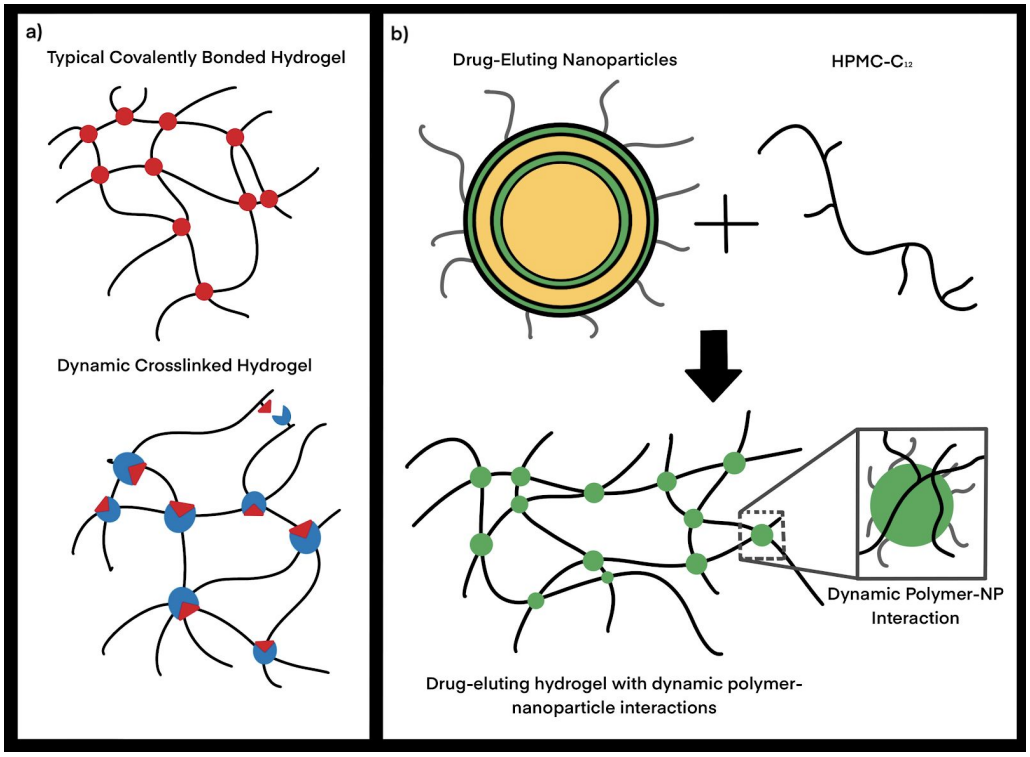

Figure 4. Dynamic properties of PerGel. a) Typical hydrogels with covalent bonds are unable to break bonds without compromising structural integrity. PeriGel uses dynamic cross-linking to allow bonds to break and reform quickly. b) The indomethacin-eluting nanoparticles within PeriGel work to form these dynamic interactions within the hydrogel and local drug delivery.

Biocompatibility

PeriGel will degrade within the body in 14-28 days without any adverse events, such as cytotoxicity or pyrogenicity, and its primary method of excretion is through the kidneys. PeriGel

will significantly reduce Grade 2 and 3 (moderate to severe) pericardial adhesions compared to currently-approved pericardial adhesion barriers.

How is PeriGel a better product than the current treatments available?

PeriGel offers greater reduction in post-operative cardiac adhesions compared to the best available alternatives. PeriGel completely prevents adhesion formations in greater than 50% of patients, where REPEL-CV completely prevented adhesions in only 1.8% of their patients[7]. PeriGel can reduce Grade 3 adhesions, defined as dense, cohesive adhesions with significant restriction of cardiac movement in greater than 85% of patients. Clinical tests with REPEL-CV show Grade 3 adhesions in 30.4% of their patients at the time of evaluation. The clinical performance of Seprafilm was even worse, with 53% of patients showing adhesions upon post-surgical evaluation[13]. *Figure 5* presents a comparison between these other solutions and PeriGel.

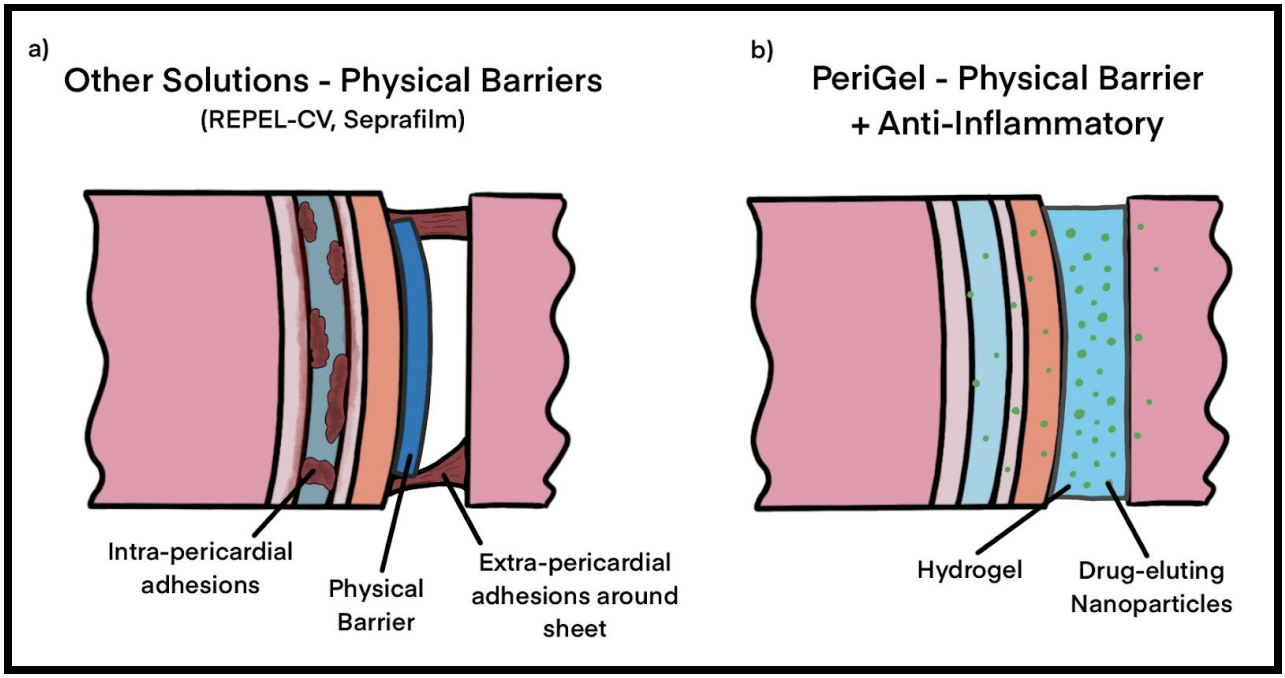

Figure 5. Comparison of other pericardial adhesion barriers and PeriGel. a) Other adhesion prevention barriers act only as a physical barrier. During biodegradation, these barriers are compromised and allow adhesions to form. b) PeriGel uses indomethacin-eluting nanoparticles to combat adhesions even during biodegradation.

Application

Open-chest surgeries will not require significant protocol modifications to use PeriGel. There is no preparation time needed compared to other available media, such as REPEL-CV or Seprafilm, which needs to be pre-soaked and trimmed prior to placement. With PeriGel, simply apply the amount needed to cover the pericardium, in layers, until the desired coverage is achieved. PeriGel is applied to the pericardial surface using a specially-modified syringe with a compressed-gas inlet. The compressed gas pressurizes the PeriGel into a liquid-like state that is easily sprayed during surgery. *Figure 6* shows the application of PeriGel to the pericardium.

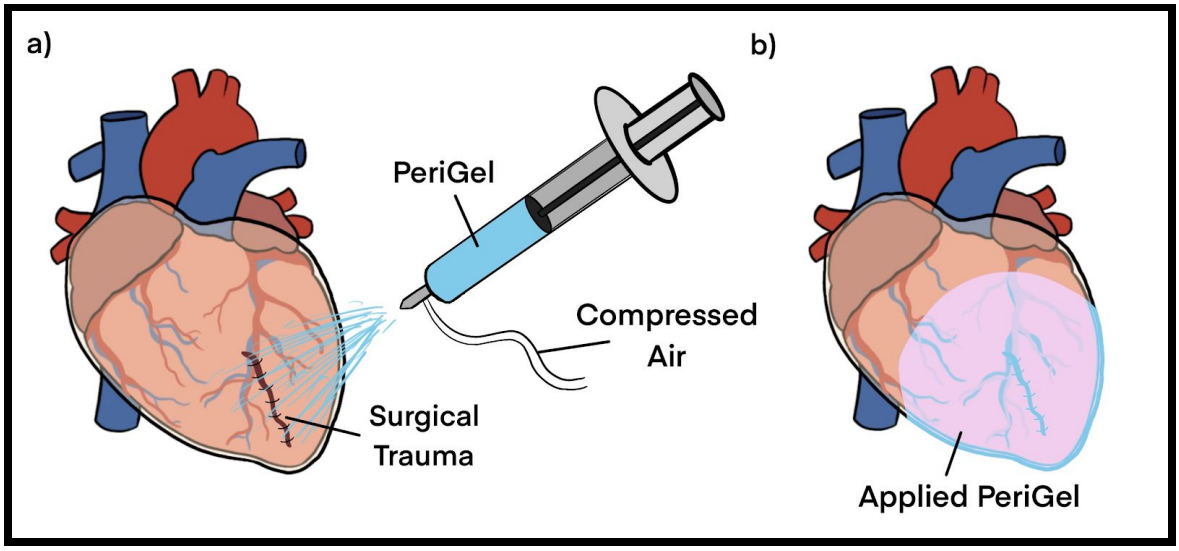

Figure 6. PeriGel application. a) PeriGel is applied to the pericardial surface under pressure using compressed air. Pressurization allows PeriGel to liquefy for easy surgical application. b) The applied PeriGel adheres to the tissue and gelifies within 5 seconds of application.

PeriGel: Improving Lives

PeriGel offers a better quality of life for the patient after surgery. A reduction in the prevalence and severity of post-operative adhesions means a reduction in the number of complications after surgery. This means fewer re-sternotomies to address the adhesions and

fewer internal complications, such as cardiac or respiratory restriction. As risk of death is increased during open-chest surgery, fewer complications will lead to fewer subsequent surgeries, which in turn will lead to fewer deaths during surgery and less suffering in the community.

Widespread adoption of PeriGel can lead to even greater benefits for society as a whole. Lower healthcare costs over time due to lower rates of complications mean lower insurance rates for those requiring the surgery. With healthcare costs continuing to rise, the prevention of surgical complications such as the formation of pericardial adhesions is an important approach to limit the rise of such costs.

PeriGel is a new, innovative method to limit the formation of pericardial adhesions. Through the use of nanotechnology, PeriGel stops adhesions from forming before they start and is easily absorbed by the body when it is no longer needed. If you are a patient in need of open-chest surgery, or you are a doctor performing these surgeries, PeriGel is the best solution to prevent pericardial adhesions after surgery.

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