BIOLOGICAL PATCH FOR THORACIC SURGERY AND PREPARATION METHOD THEREFOR

TECHNICAL FIELD

[0001] The present invention relates to a biological patch for thoracic surgery and a preparation method therefor.

BACKGROUND

[0002] Lung volume reduction surgery is an effective treatment for intrapulmonary or bronchial diseases, including wedge resection and local resection of the lung, resection of lower esophageal carcinoma, pulmonary pleurectomy, pneumonectomy, lobectomy, and segmentectomy. Persistent air leakage after surgery is critical to the success of lung volume reduction surgery and a major cause of impaired pulmonary function and other complications. The National Expert Consensus on the Management of Persistent Air Leakage During the Perioperative Period of Thoracic Surgery (2023) recommends the use of appropriate surgical techniques to minimize or avoid visceral pleural rupture. For patients with high-risk factors such as chronic obstructive pulmonary disease (COPD) or emphysema undergoing pulmonary surgery, biological patches for thoracic surgeries with relevant indications can be used routinely after preoperative evaluation to prevent pulmonary air leakage (Grade 1B recommendation; 97% expert agreement).

[0003] Currently, although commercially available biological patches for thoracic surgeries reduce pulmonary air leakage to a certain extent, the problem of air leakage persists. Therefore, higher performance requirements are imposed on biological patches for thoracic surgeries in clinical practice. The biological patches are required to have better compliance, resistance to tissue slippage, and excellent fitting performance, so as to reduce surgical difficulty and postoperative complications, and minimize intraoperative and postoperative air leakage with improved technologies and products.

SUMMARY

[0004] The present invention finds through research that a biological patch with excellent resilience and compliance can be obtained by controlling four key parameters of the biological patch within specific ranges, namely maximum tensile elongation, elastic strain, single-suture tensile force, and the ratio of elastic strain to maximum tensile elongation. Such a patch can effectively prevent pulmonary air leakage in thoracic surgery.

[0005] In the present invention, the determination of maximum tensile elongation and single-suture tensile force refers to the existing literature (Li Chongchong, Liu Li, Wang Shuo, et al. Comparison of mechanical properties of allogeneic and animal-derived patches[J]. Beijing Biomedical Engineering, 2021). The elastic strain is determined by a conventional method in the art. The prepared biological patch is cut into a strip of 4 cm in length and 1 cm in width, clamped on a tensile testing machine along its length, and stretched at a speed of 100 mm/min until fracture. A tensile curve is plotted, and the elastic strain of the biological patch is calculated based on the elastic deformation segment of the tensile curve.

[0006] In one aspect, the present invention relates to a biological patch for thoracic surgery, wherein the biological patch has a maximum tensile elongation greater than 17.2%, an elastic strain greater than 18.3%, and a single-suture tensile force greater than 15.5 N.

[0007] Preferably, the maximum tensile elongation of the biological patch is 17.2–51.9%.

[0008] Preferably, the elastic strain of the biological patch ranges from 18.3% to 39.4%.

[0009] Preferably, the single-suture tensile force of the biological patch is 15.5–33.4 N.

[0010] Preferably, the ratio of elastic strain to maximum tensile elongation of the biological patch is 49–93%.

[0011] Preferably, the biological patch has a maximum tensile elongation of 25.6–51.9%, a single-suture tensile force of 17.2–33.4 N, an elastic strain of 18.3–39.4%, and a ratio of elastic strain to maximum tensile elongation of 49–93%.

[0012] Preferably, the biological patch for thoracic surgery is provided with two perforations located at opposite ends of the biological patch.

[0013] In another aspect, the present invention relates to a stapler kit comprising the above biological patch for thoracic surgery. Since most cutting procedures in current lung volume reduction surgery adopt cutting staplers, the application of the patch requires pre-installation with the staple cartridge of the stapler, i.e., the patch is stretched and fixed to both ends of the staple cartridge before surgery.

[0014] In another aspect, the present invention relates to a method for preparing the above biological patch for thoracic surgery, comprising:

[0015] (1) Pretreatment:

[0016] ① Immersing healthy bovine pericardial tissue sheets in hypotonic Hank's solution, rinsing repeatedly with fresh hypotonic Hank's solution for multiple times to remove swollen and broken cell debris, nuclei, and organelles after decellularization;

[0017] ② Rinsing the treated tissue sheets repeatedly with physiological saline for 90–150 min each time, replacing the saline each time, until no visible cells, cellular components, or cell debris are observed under a microscope, and soluble proteins and nucleic acids are undetectable by quantitative determination;

[0018] ③ Removing phospholipids, non-structural proteins, and part of the tissue matrix from the tissue sheets with a surfactant solution; the surfactant solution may be Tween 80, sodium dodecyl sulfate (SDS), or Triton X-100;

[0019] ④ Soaking in 2.5–4% glutaraldehyde solution for 3–3.5 h;

[0020] (2) Chemical modification:

[0021] Placing the pretreated tissue material in a chromic hydroxide solution with a Cr^{3+} concentration of 0.0625 mol/dm³ and an OH/Cr ratio of 0.5 for the first water-bath oscillation at 20–28 °C for 2–4 h, adjusting the pH of the treatment solution by 0.3–0.6 units with 10% $NaHCO_3$, followed by a second water-bath oscillation at 32–40 °C for 3–5 h to obtain a single-layer sheet-shaped biological patch.

[0022] The present invention obtains a biological patch for thoracic surgery with good biocompatibility, capable of integrating with the patient's lung tissue, and meeting the anti-calcification and biomechanical properties required for therapeutic effects through decellularization, immunogenicity removal, and chemical modification of bovine pericardial tissue.

[0023] When clamping tissue, the staple holes and suture sites formed after titanium staples of the stapler penetrate the biological patch shrink rapidly due to the elastic retraction deformation of the patch to prevent air leakage. Meanwhile, the resilient deformation of the patch makes tissue clamping more stable and firmer.

[0024] In lung volume reduction surgery, the biological patch for thoracic surgery can be used for lining and sealing the incision margins of lung and tracheal tissues. It not only ensures stable

fitting with lung tissue without slippage or postoperative air leakage, but also promotes healing and repair of incision margin tissues, reduces postoperative adhesions and pain, greatly improves patient comfort, reduces foreign body sensation, significantly enhances postoperative quality of life, and effectively prevents complications such as large-area subcutaneous emphysema, dyspnea, pulmonary infection, incision infection, and empyema caused by air leakage after lung volume reduction surgery.

[0025] One side of the biological patch for thoracic surgery provided by the present invention is a rough surface, and the other side is a smooth surface. The rough surface has high friction after contacting the staple cartridge or anvil of the stapler, making the patch less prone to slippage during cutting and stapling. After installation, the smooth surface fits the lung tissue with excellent fitting performance, improving patient comfort and reducing foreign body sensation. Implantation of the biological patch for thoracic surgery provided by the present invention during surgery results in an overall reinforced lung tissue incision margin through tissue fusion and remodeling, and the remodeled lung tissue has normal blood transport.

[0026] The biological patch for thoracic surgery provided by the present invention has excellent mechanical properties and can effectively prevent intraoperative and postoperative air leakage in patients, especially those with poor lung quality due to COPD (Chronic Obstructive Pulmonary Disease), long-term smoking, radiotherapy, or chemotherapy. Pulmonary air leakage may occur due to mismatched staple forming height and tissue thickness. The staple forming height is fixed, but the thickness of lung tissue varies among patients and at different sites. Air leakage may occur after cutting and suturing when the lung tissue is too thick or too thin relative to the staple height. The biological patch for thoracic surgery provided by the present invention has excellent resilience and toughness, meeting the biomechanical requirements for treating patients of different ages and conditions. After clamping tissue, the staple holes and suture sites shrink rapidly due to elastic retraction to prevent leakage, and the resilient deformation of the patch ensures stable tissue clamping and prevents postoperative air leakage.

[0027] Compared with biological patches made of the polymer synthetic material polyglycolic acid, after implantation of the biological patch for thoracic surgery of the present invention, the patient's autologous tissue cells continuously infiltrate into the patch. The infiltrated tissue cells proliferate and differentiate, and mature fibroblasts secrete collagen. The proliferation of collagen tissue thickens the weakened lung tissue, and small blood vessels form in the patch. With the fusion and remodeling of the patch and autologous lung tissue, the lung tissue at the cutting and suturing site is strengthened more rapidly and durably.

[0028] The biological patch for thoracic surgery prepared by the process of the present invention removes the immunogenicity of the tissue sheet, retains the scaffold of natural biological tissue and part of the tissue matrix, has good biocompatibility for fusion and remodeling with the patient's lung tissue, facilitates host cell infiltration and tissue remodeling, and is suitable for repairing various soft tissues.

BRIEF DESCRIPTION OF THE DRAWINGS

[0029] Fig. 1 is a schematic diagram of pre-installing the biological patch on a stapler; wherein A shows biological patches with different perforation distances; B shows a stapler without a pre-installed biological patch; C shows a stapler with a pre-installed biological patch; D is an enlarged view of part E in Fig. C.

[0030] Reference signs: biological patch 1, perforation 2, stapler 3, clamping piece 4, staple cartridge or titanium staple anvil 5.

DETAILED DESCRIPTION OF THE EMBODIMENTS

[0031] The present invention is further described in detail below through specific embodiments:

[0032] In the process of completing the present invention, the inventor first took tensile strength, maximum tensile elongation, and single-suture tensile force of the biological patch as parameters for screening patches to address the problem of frequent pulmonary air leakage in thoracic surgery, referring to the existing literature (Li Chongchong, Liu Li, Wang Shuo, et al. Comparison of mechanical properties of allogeneic and animal-derived patches[J]. Beijing Biomedical Engineering, 2021). However, after measurement, it was found that the tensile strength of the obtained biological patches fluctuated greatly and was unstable. Moreover, animal experiments showed that the correlation between tensile strength and pulmonary air leakage was unstable, so tensile strength could not be used as a screening parameter for biological patches. Therefore, the inventor determined the screening parameters as maximum tensile elongation, elastic strain, and single-suture tensile force, and confirmed the optimal ranges of these three parameters through clinical trials: maximum tensile elongation 17.2–51.9%, elastic strain 18.3–39.4%, and single-suture tensile force 15.5–33.4 N. During this process, the inventor unexpectedly found that the ratio of elastic strain to maximum tensile elongation also affected pulmonary air leakage.

[0033] The inventor verified this finding through clinical trials and confirmed that controlling the ratio of elastic strain to maximum tensile elongation to be no less than 49% on the basis of specific ranges of maximum tensile elongation, elastic strain, and single-suture tensile force is beneficial to preventing pulmonary air leakage in thoracic surgery.

[0034] I. Preparation Method of the Biological Patch

[0035] (1) Pretreatment

[0036] In the present invention, pretreatment specifically refers to the steps of decellularization and immunogenicity removal of biological tissue, which are conventional techniques in the art aiming to remove cellular components and immunogenicity. The present invention does not limit the specific operation process, which can refer to the following:

[0037] ① Immersing healthy bovine pericardial tissue sheets in hypotonic Hank's solution, rinsing repeatedly with fresh hypotonic Hank's solution for multiple times to fully swell and break various cells in the tissue, and remove swollen and broken cell debris, nuclei, and organelles after decellularization;

[0038] ② Rinsing the treated tissue sheets repeatedly with physiological saline for 90–150 min each time, replacing the saline each time, until no visible cells, cellular components, or cell debris are observed under a microscope, and soluble proteins and nucleic acids are undetectable by quantitative determination; for example, the rinsing time is preferably 90 min in a specific embodiment of the present invention;

[0039] ③ Removing phospholipids, non-structural proteins, and part of the tissue matrix such as hyaluronic acid, various chondroitin sulfates, and mucopolysaccharides (immunogenic molecules) from the tissue sheets with a surfactant solution; the surfactant solution may be Tween 80, SDS, or Triton X-100; for example, Tween 80 is preferably used in a specific embodiment of the present invention;

[0040] ④ Soaking in 2.5–4% glutaraldehyde solution for 3–3.5 h; for example, the soaking condition is preferably 2.5% glutaraldehyde solution for 3 h in a specific embodiment of the

present invention.

[0041] (2) Chemical modification

[0042] Composite cross-linking modification is performed on free carboxyl groups within and/or between collagen molecules of the tissue scaffold and between the scaffold collagen and tissue matrix, using a polymer of chromic hydroxide coordination compound as the cross-linking agent, so that the modified tissue sheet obtains corresponding mechanical properties and anti-calcification properties. For specific operations, refer to: placing the pretreated tissue material in a chromic hydroxide solution with a Cr^{3+} concentration of 0.0625 mol/dm³ and an OH/Cr ratio of 0.5 for the first water-bath oscillation at 20–28 °C for 2–4 h; for example, the first water-bath oscillation condition is preferably 20 °C for 2 h in a specific embodiment of the present invention.

[0043] Adjust the pH of the treatment solution by 0.3–0.6 units with 10% $NaHCO_3$, followed by a second water-bath oscillation at 32–40 °C for 3–5 h to obtain a single-layer sheet-shaped biological patch; for example, the second water-bath oscillation condition is preferably adjusting the pH by 0.3 units with 10% $NaHCO_3$ and then oscillating at 32 °C for 3 h in a specific embodiment of the present invention.

[0044] The obtained biological patch has a rough surface on one side and a smooth surface on the other. As shown in Fig. 1, two or more perforations 2 with the same orientation and a size slightly smaller than the width of the clamping piece 4 are formed on the biological patch 1, so that the free end of the clamping piece 4 passes through two of the perforations 2 in sequence (the distance between the two perforations 2 is selected according to surgical needs). The position of the biological patch 1 is manually adjusted to make it flatly fit the inner side of the clamping piece 4. The rough surface contacts the staple cartridge or anvil 5 of the stapler with high friction, preventing the biological patch 1 from slipping during cutting and stapling; the smooth surface fits the lung tissue to ensure good fitting. The size of the perforations 2 slightly smaller than the width of the clamping piece 4 ensures that the biological patch 1 remains stretched when hung on the clamping piece 4 without sliding or falling off.

[0045] Examples 1–24

[0046] The main differences in the preparation process of the biological patches in Examples 1–24 are shown in Table 1 below.

Table 1 Main Differences in Preparation Methods of Examples 1–24

Group	First Water-Bath Oscillation Condition	Second Water-Bath Oscillation Condition	pH Increase by $NaHCO_3$	Saline Rinsing Time per Time	Surfactant Type	Glutaraldehyde Concentration and Soaking Time
Example 1	20 °C, 2 h	32 °C, 3 h	0.3	90 min	Tween 80	2.5%, 3 h
Example 2	21 °C, 2 h	34 °C, 3 h	0.3	90 min	Tween 80	2.5%, 3 h
Example 3	22 °C, 2 h	36 °C, 3 h	0.3	90 min	Tween 80	2.5%, 3 h
Example 4	23 °C, 2 h	38 °C, 3 h	0.3	90 min	Tween 80	2.5%, 3 h
Example 5	24 °C, 2 h	40 °C, 3 h	0.3	90 min	Tween 80	2.5%, 3 h
Example 6	25 °C, 2 h	32 °C, 3.5 h	0.3	90 min	Tween 80	2.5%, 3 h
Example 7	26 °C, 2 h	34 °C, 3.5 h	0.3	90 min	Tween 80	2.5%, 3 h

Example 8	27 °C, 2 h	36 °C, 3.5 h	0.3	90 min	Tween 80	2.5%, 3 h
Example 9	21 °C, 2.5 h	38 °C, 3.5 h	0.3	90 min	Tween 80	2.5%, 3 h
Example 10	22 °C, 2.5 h	40 °C, 3.5 h	0.3	90 min	Tween 80	2.5%, 3 h
Example 11	23 °C, 2.5 h	32 °C, 4 h	0.3	90 min	Tween 80	2.5%, 3 h
Example 12	24 °C, 2.5 h	34 °C, 4 h	0.3	90 min	Tween 80	2.5%, 3 h
Example 13	25 °C, 2.5 h	36 °C, 4 h	0.3	90 min	Tween 80	2.5%, 3 h
Example 14	26 °C, 2.5 h	38 °C, 4 h	0.4	90 min	Tween 80	2.5%, 3 h
Example 15	27 °C, 2.5 h	40 °C, 4.5 h	0.5	90 min	Tween 80	2.5%, 3 h
Example 16	28 °C, 2.5 h	32 °C, 4.5 h	0.6	90 min	Tween 80	2.5%, 3 h
Example 17	22 °C, 3 h	34 °C, 4.5 h	0.6	100 min	Tween 80	2.5%, 3 h
Example 18	24 °C, 3 h	36 °C, 4.5 h	0.6	120 min	Tween 80	2.5%, 3 h
Example 19	25 °C, 3 h	38 °C, 4.5 h	0.6	150 min	Tween 80	2.5%, 3 h
Example 20	28 °C, 3 h	40 °C, 4.5 h	0.6	150 min	SDS	2.5%, 3 h
Example 21	22 °C, 4 h	32 °C, 5 h	0.6	150 min	Triton X100	2.5%, 3 h
Example 22	24 °C, 4 h	34 °C, 5 h	0.6	150 min	Tween 80	3%, 3 h
Example 23	26 °C, 4 h	36 °C, 5 h	0.6	150 min	Tween 80	3.5%, 3 h
Example 24	28 °C, 4 h	38 °C, 5 h	0.6	150 min	Tween 80	4%, 3.5 h

[0047] II. Determination of Tensile Strength, Maximum Tensile Elongation, and Single-Suture Tensile Force

[0048] Good mechanical properties can reduce or even avoid pulmonary air leakage, reduce postoperative complications, improve patch compliance, and enhance patient comfort. To explore the relationship between mechanical parameters and air leakage, compliance, and comfort of biological patches for thoracic surgeries, the inventor first consulted literature and determined the tensile strength, maximum tensile elongation, and single-suture tensile force of the biological patches obtained in Examples 1–24 (10 patches per example, parameters measured respectively with reference to the literature, average values taken) (Li Chongchong, Liu Li, Wang Shuo, et al. Comparison of mechanical properties of allogeneic and animal-derived patches[J]. Beijing Biomedical Engineering, 2021). The results are shown in Table 2 below.

Table 2 Maximum Tensile Elongation, Tensile Strength, and Single-Suture Tensile Force of Examples 1–24

Group	Maximum Tensile Elongation	Tensile Strength	Single-Suture Tensile Force
Example 1	37.7±1.3%	24.7±3.2 MPa	17.2±0.5 N
Example 2	38.1±0.3%	16.3±2.2 MPa	12.5±0.1 N

Example 3	17.2±0.2%	20.2±2.5 MPa	5.1±0.3 N
Example 4	25.6±0.6%	24.3±3.1 MPa	20.3±0.9 N
Example 5	33.2±0.1%	23.2±1.6 MPa	21.5±0.2 N
Example 6	49.1±0.6%	31.8±2.1 MPa	25.7±0.4 N
Example 7	32.1±0.2%	39.5±3.1 MPa	21.2±0.7 N
Example 8	35.7±0.3%	26.2±4.7 MPa	27.5±0.1 N
Example 9	47.2±0.3%	27.8±1.5 MPa	27.1±1.1 N
Example 10	42.5±0.2%	27.3±6.1 MPa	28.6±0.3 N
Example 11	31.4±0.1%	30.7±2.6 MPa	30.7±0.1 N
Example 12	51.9±0.2%	19.1±4.9 MPa	27.2±0.8 N
Example 13	37.3±0.1%	32.9±5.2 MPa	33.4±0.3 N
Example 14	16.3±0.5%	21.3±4.1 MPa	15.3±0.9 N
Example 15	18.8±0.3%	25.4±1.9 MPa	21.8±0.6 N
Example 16	33.4±0.9%	25.5±3.3 MPa	14.9±0.3 N
Example 17	20.3±0.2%	20.4±5.3 MPa	17.7±0.1 N
Example 18	26.1±1.1%	21.6±3.4 MPa	25.2±1.0 N
Example 19	35.6±0.4%	19.5±2.3 MPa	15.5±0.5 N
Example 20	37.8±0.3%	22.9±1.4 MPa	21.4±0.2 N
Example 21	15.6±0.1%	24.6±3.3 MPa	25.2±1.7 N
Example 22	39.7±1.2%	29.5±1.6 MPa	32.7±0.1 N
Example 23	33.1±0.2%	33.2±4.1 MPa	25.6±1.3 N
Example 24	37.5±0.2%	33.7±4.2 MPa	29.1±1.3 N

[0049] It can be concluded from Table 2 that the tensile strength of the 10 biological patches obtained in each of Examples 1–24 fluctuates greatly and is unstable, which may be due to other unobserved influencing factors, making accurate control of tensile strength unsuitable for surgical materials.

[0050] The biological patches obtained in Examples 1–24 have a maximum tensile elongation of 15.6–51.9%, a tensile strength of 16.3–39.5 MPa, and a single-suture tensile force of 5.1–33.4 N.

[0051] Ten biological patches were obtained for each example, cut into 4 cm×1 cm strips, and tested for pre-installation on a stapler.

[0052] Pre-installation of the biological patch on the stapler requires proper stretching, which is related to maximum tensile elongation. Theoretically, a higher maximum tensile elongation is better; if it is too low, the patch will break after a small stretch. Specifically, 10 patches from Example 21 (maximum tensile elongation 15.6±0.1%) were assembled on a stapler, 9 broke and 1 showed obvious cracks. Ten patches from Example 14 (maximum tensile elongation 16.3±0.5%) were assembled, 7 broke and 3 showed obvious cracks. This reflects the high toughness of the biological patch; the patch is extremely resistant to deformation, and after deformation is generated, it is rapidly transitioned into permanent deformation and is quickly subjected to fracture failure.

[0053] Thus, biological patches with maximum tensile elongation of 15.6% and 16.3% cannot meet stapler installation requirements. Based on other examples meeting stretching requirements, the minimum maximum tensile elongation for stapler installation is 17.2±0.2% (Example 3).

[0054] Animal experiments were performed on examples meeting stapler pre-installation requirements (Examples 1–13, 15–20, 22–24).

[0055] III. Animal Experiments

[0056] White pigs are ideal animal models for studying human lung diseases and injuries due to many similarities in lung anatomy and physiology to humans, with moderate size for easy operation and management. Compared with small animals such as mice and rats, white pigs provide larger operating space for easier surgery. They are easy to raise and manage under laboratory conditions, with low postoperative infection risk, easy long-term feeding control, and high long-term survival rate.

[0057] Healthy experimental animals were purchased in accordance with SOP-5 Operational Procedures for Laboratory Animals and Receipt, provided by Jiangsu Yinse Biotechnology Co., Ltd. (License No. SCXK (Gan) 2023-0002). All animals were used for the first time in animal experiments at the start of the test and passed quarantine before grouping.

[0058] 1. Inclusion Criteria

[0059] Meet the national Administrative Measures for the Quarantine of Laboratory Animals; body weight 50–60 kg; normal physiological indicators; no obvious serious animal diseases.

[0060] 2. Feeding

[0061] Laboratory animals were managed in accordance with SMP-5 Rules for the Care and Management of Laboratory Animals. Feed was given twice daily, and water was available ad libitum via an automatic water supply system. Feed and water were clean and safe.

[0062] 3. Grouping and Quantity

[0063] 1-month experimental group: 110 pigs; 3-month experimental group: 110 pigs; male and female, randomly grouped. A total of 22 examples (Examples 1–13, 15–20, 22–24), 10 pigs per example (5 for 1-month group, 5 for 3-month group), 1 patch per pig.

[0064] Animal information was recorded during the experiment: body weight, operation time, survival days, patch information, etc.

[0065] Routine blood, blood biochemistry, coagulation function, and blood gas were measured preoperatively and at 1 and 3 months postoperatively.

[0066] 4. Experimental Steps

[0067] ① Preoperative preparation; ② Preoperative blood tests and data recording; ③ General anesthesia, tracheal intubation, ventilator-assisted ventilation, disinfection and skin preparation; ④ Supine position, laparotomy to expose the abdomen, isolate lung tissue, select a

suitable site, make an incision; ⑤ Install a 4 cm×1 cm biological patch on a disposable stapler, place the stapler with pre-installed patch at the predetermined site, adjust angle and depth to ensure close fitting with surrounding tissue; ⑥ Carefully inspect the anastomosis and patch, check patch fixation, fitting with lung tissue, and resilience; pour warm saline into the thoracic cavity to observe air leakage at staple holes and suture sites; close the abdomen after confirming no air leakage.

[0068] Postoperatively, animals were sent to the observation room, supported by a ventilator until awakening, and then transferred to the animal room after standing. 12h/12h alternating lighting, feed once daily in the morning and afternoon, free drinking water. Daily observation of mental state, appetite, respiration, wound complications, and other adverse symptoms.

[0069] Ceftriaxone sodium 2g was intramuscularly injected for 1 week postoperatively for anti-infection. Daily observation of mental state, appetite, respiration, incision healing, nausea, vomiting, subcutaneous emphysema, dyspnea, pulmonary infection, incision infection, empyema, etc. Incision disinfection with iodophor until healing. Regular physical examinations and blood tests by veterinarians, anti-infection prophylaxis and treatment based on results. Postoperative medication and 24h adverse events (including death, infection) were recorded.

[0070] At the end of the experiment, gross observation was performed to check patch integrity, defects, air leakage, surface thrombosis, and surrounding tissue hemorrhage or necrosis.

[0071] 5. Animal Experiment Evaluation Criteria

[0072] ① Intraoperative and postoperative air leakage at the anastomosis and surrounding tissue; ② Close fitting of the patch at the anastomosis; ③ Incidence of postoperative complications such as infection and rejection during feeding; ④ Gross specimen observation: animals were sacrificed at 1 and 3 months postoperatively to observe anastomosis healing and patch-promoted tissue regeneration and repair; ⑤ Histological examination: patch and tissue specimens were collected at 1 and 3 months postoperatively for histological examination to observe thromboembolism, inflammation, necrosis, etc.

[0073] 6. Animal Experiment Results

[0074] (1) A maximum tensile elongation of 17.2–51.9% meets stapler installation requirements.

[0075] Pigs implanted with patches from 13 examples (Examples 1, 4–6, 8–13, 18, 23–24) showed no pulmonary air leakage.

[0076] The surgery was successfully completed without air leakage, the patch fitted closely with lung tissue, and the resection margin was intact without air leakage or exudate. At 1 and 3 months follow-up, scar tissue formed at the lung resection margin without degradation, indicating that the patch acts as a scaffold to promote repair and healing of the lung resection margin, showing good biocompatibility, integration with surrounding tissue, and promotion of repair.

[0077] Intraoperative vital signs of anesthetized animals were normal without adverse events.

[0078] Postoperative routine blood tests showed normal cell count, morphology, and quality; stable leukocytes, erythrocytes, hemoglobin, and platelets without abnormal indicators. Liver and kidney function values were within the normal range without abnormalities.

[0079] Animals survived in good condition with normal body temperature, diet, excretion, and autonomous activities, no obvious weight loss, fever, anorexia, or mania, and survived to the end point.

[0080] (2) Single-suture tensile force reflects the shear resistance of the patch. Too low a force causes tearing at staple holes and suture sites. Obvious tearing occurred at staple holes of patches from Example 3 (5.1±0.3 N), Example 2 (12.5±0.1 N), and Example 16 (14.9±0.3 N), with worsening tearing over time. No obvious tearing was observed in Example 19 (15.5±0.5 N), indicating that the single-suture tensile force should be no less than 15.5 N (15.5–33.4 N) to avoid tearing when fixed with titanium staples.

[0081] (3) Theoretically, proper tensile strength helps ensure patch compliance and prevent air leakage. However, animal experiments showed:

[0082] Pulmonary air leakage occurred in patches from Examples 2, 3, 7, 15–17, 19, 20, 22.

[0083] Specifically, air leakage occurred in patches from Example 2 (16.3±2.2 MPa), Example 19 (19.5±2.3 MPa), Example 3 (20.2±2.5 MPa), Example 17 (20.4±5.3 MPa), Example 20 (22.9±1.4 MPa), Example 15 (25.4±1.9 MPa), Example 16 (25.5±3.3 MPa), Example 22 (29.5±1.6 MPa), and Example 7 (39.5±3.1 MPa).

[0084] However, examples with similar tensile strength showed no air leakage, e.g., Example 12 (19.1±4.9 MPa) and Example 18 (21.6±3.4 MPa) vs. Example 19 and Example 3; Example 4 (24.3±3.1 MPa) and Example 8 (26.2±4.7 MPa) vs. Example 15 and Example 16; Example 6 (31.8±2.1 MPa), Example 9 (27.8±1.5 MPa), Example 11 (30.7±2.6 MPa), Example 23 (33.2±4.1 MPa), and Example 24 (33.7±4.2 MPa) vs. Example 22 and Example 7.

[0085] Since the correlation between tensile strength and air leakage is unstable, new mechanical parameters indicating air leakage are needed.

[0086] Based on years of research on applying animal-derived biological materials to thoracic surgery implantation, the inventor found that mismatched staple forming height and tissue thickness is a major cause of pulmonary air leakage. The staple forming height is fixed, but lung tissue thickness varies among patients and sites, leading to air leakage at the resection margin. Therefore, the patch needs good resilience. The inventor introduced "elastic strain" instead of "tensile strength" and explored air leakage prevention by combining elastic strain, maximum tensile elongation, and single-suture tensile force.

[0087] IV. Determination of Elastic strain

[0088] 1. Determination Method

[0089] A 4 cm×1 cm patch strip was clamped on a tensile testing machine along its length, stretched at 100 mm/min until fracture. A tensile curve was plotted, and the elastic strain was calculated based on the elastic deformation segment.

[0090] 2. Results

Table 3 Elastic strain of Examples 1–24

Group	Elastic strain	Group	Elastic strain
Example 1	34.9±0.7%	Example 13	20.5±0.2%
Example 2	15.6±0.2%	Example 14	11.8±0.1%
Example 3	8.9±0.1%	Example 15	17.2±1.9%
Example 4	19.1±0.2%	Example 16	10.3±1.6%
Example 5	29.2±0.4%	Example 17	17.5±0.6%
Example 6	19.9±1.1%	Example 18	18.8±0.1%

Example 7	16.2±1.1%	Example 19	15.4±0.7%
Example 8	23.2±0.5%	Example 20	12.7±0.1%
Example 9	39.4±0.9%	Example 21	12.6±0.3%
Example 10	25.1±0.1%	Example 22	14.9±0.4%
Example 11	18.3±0.2%	Example 23	28.1±0.1%
Example 12	32.6±0.3%	Example 24	18.4±0.3%

[0091] It can be seen from Table 3 that the elastic strain of patches from Examples 1–24 is stable, ranging from 8.9% to 39.4%.

[0092] Except for air leakage caused by tearing at staple holes and suture sites in Examples 2, 3, and 16, animal experiments unexpectedly showed that 7 pigs in total developed air leakage with patches from Example 20 (12.7±0.1%) and Example 22 (14.9±0.4%); 4 pigs with Example 19 (15.4±0.7%) and Example 7 (16.2±1.1%); 3 pigs with Example 15 (17.2±1.9%); and 1 pig with Example 17 (17.5±0.6%). The number of pigs with air leakage decreased as the elastic strain increased, and all these examples had lower elastic strains than those without air leakage.

[0093] Thus, the inventor inferred that a higher elastic strain reduces air leakage risk. Animal experiments preliminarily confirmed the validity of introducing "elastic strain", and air leakage was attributed to poor resilience, poor tissue fitting, and insufficient shrinkage elasticity at staple holes and suture sites.

[0094] Based on animal experiments, the elastic strain of the biological patch is preliminarily determined to be 18.3–39.4%.

[0095] V. Clinical Trial I

[0096] 1. Inclusion Criteria, Exclusion Criteria, and Clinical Data Collection

[0097] (1) Inclusion Criteria

[0098] ① Age 18–75 years, male or female; ② Meeting clinical surgical indications for lung volume reduction surgery including various pulmonary resections (any surgical approach: open, laparoscopic, robotic); ③ Able to understand the trial purpose, voluntarily participate and sign informed consent, willing to undergo relevant examinations and follow-up.

[0099] (2) Exclusion Criteria

[0100] ① Patients requiring ICU ventilator support postoperatively; ② Patients converted to open surgery due to intraoperative bleeding or severe pleural adhesions; ③ Postoperative diagnosis of bronchopleural fistula; ④ Death during hospitalization or incomplete clinical data.

[0101] (3) Clinical Data Collection

[0102] Data of eligible patients were collected: ① Demographic data: gender, age, BMI, smoking history; ② Preoperative evaluation: pulmonary function (FEV1%, FEV1%/FVC%), peripheral blood lymphocyte count, albumin, prognostic nutritional index (PNI); ③ Surgical data: surgical site, surgical method (lobectomy or segmentectomy), lymph node dissection, pleural adhesions, pathological results (benign/malignant), air leakage by water test and lung inflation; ④ Postoperative stage: daily air leakage assessment, pleural cavity pressure difference at 12h postoperatively.

[0103] 2. Trial Grouping

[0104] Test group: 13 subgroups using patches from 13 examples meeting animal experiment standards, 10 patients per subgroup, undergoing lung volume reduction surgery with the patch pre-installed on the stapler.

[0105] Control group: Patients undergoing surgery with stapler closure/anastomosis only.

[0106] 3. Trial Procedure

[0107] (1) Sign informed consent; (2) Case screening, confirm inclusion/exclusion criteria, and collect baseline data; (3) Confirm surgery time; (4) Random grouping into test or control group; (5) Perform surgery; (6) Observe and record air leakage in the surgical report; (7) Evaluate postoperative condition; (8) Complete follow-up before discharge, 1 month, and 3 months postoperatively as per the protocol.

[0108] All patients underwent surgery under general anesthesia. The diseased lung was closed and resected with a stapler, the bronchus was transected with a stapler, and hemostasis was completed. Warm saline was infused into the thoracic cavity for irrigation, and lung inflation was performed to observe air leakage from lung tissue and bronchial stumps. Leaky lung wounds or bronchial stumps were reinforced with absorbable sutures, and air leakage was rechecked before chest closure. One or two thoracic closed drainage tubes reaching the pleural apex were placed postoperatively and connected to a drainage bottle containing 500 ml saline. Postoperative air leakage was monitored, and symptomatic treatment (oxygen inhalation, nebulization, expectorant, anti-asthma, nutritional support, anti-infection) was given.

[0109] 4. Trial Method

[0110] Prospective, multi-center, randomized controlled, open-label, superiority trial.

[0111] 5. Trial Results

[0112] (1) Baseline Data Comparison

[0113] A total of 150 eligible patients were enrolled, and air leakage is shown in Table 4.

Table 4 Results of Clinical Trial I

No.	Group	Air Leakage in Lobectomy	Air Leakage in Wedge Resection	Air Leakage in Bullectomy	Air Leakage in Other LVRS	No Leakage Total
1	Example 1	0/5	0/3	0/2	0/0	0/10
2	Example 4	0/3	0/4	0/2	0/1	0/10
3	Example 5	0/4	0/0	0/4	0/2	0/10
4	Example 6	1/2	1/4	2/4	0/0	4/10
5	Example 8	0/7	0/1	0/2	0/0	0/10
6	Example 9	0/3	0/4	0/2	0/1	0/10
7	Example 10	0/4	0/2	0/4	0/0	0/10
8	Example 11	0/1	0/2	0/4	0/3	0/10
9	Example 12	0/3	0/4	0/2	0/1	0/10
10	Example 13	0/7	0/1	0/2	0/0	0/10
11	Example 15	0/3	0/4	0/2	0/1	0/10
12	Example 17	0/3	0/4	0/2	0/1	0/10

13	Example 18	0/1	0/5	0/2	0/2	0/10
14	Example 23	0/2	0/4	0/4	0/0	0/10
15	Example 24	0/4	0/3	0/4	0/2	0/10
16	Control (stapler only)	1/1	6/8	2/10	1/1	10/20

[0114] Note: Other lung volume reduction surgeries include pneumonectomy, pulmonary pleurectomy, etc. The number before "/" is cases with air leakage; the number after "/" is total cases.

[0115] Comprehensive results of Table 4 show:

[0116] (1) Based on the previously determined ranges (maximum tensile elongation 17.2–51.9%, elastic strain 18.3–39.4%, single-suture tensile force 15.5–33.4 N), air leakage occurred in the test group using the patch from Example 6 (19.9±1.1%). Theoretically, higher elastic strain is better. The inventor inferred that the elasticity of the patch needs to be further improved to seal staple holes and suture sites and adapt to frequent lung expansion and contraction.

[0117] Further comparison of elastic strains of Example 6 (19.9±1.1%), Example 11 (18.3±0.2%), and Example 24 (18.4±0.3%) unexpectedly revealed that the ratio of elastic strain to maximum tensile elongation of Example 6 (41%) was low. The inventor inferred a correlation between this ratio and clinical outcomes, which was verified in subsequent clinical trials.

Table 5 Ratio of Elastic strain to Maximum Tensile Elongation of Examples 1–24

Group	Maximum Tensile Elongation	Elastic strain	Ratio (%)
Example 1	37.7±1.3%	34.9±0.7%	93
Example 2	38.1±0.3%	15.6±0.2%	41
Example 3	17.2±0.2%	8.9±0.1%	52
Example 4	25.6±0.6%	19.1±0.2%	75
Example 5	33.2±0.1%	29.2±0.4%	88
Example 6	49.1±0.6%	19.9±1.1%	41
Example 7	32.1±0.2%	16.2±1.1%	50
Example 8	35.7±0.3%	23.2±0.5%	65
Example 9	47.2±0.3%	39.4±0.9%	83
Example 10	42.5±0.2%	25.1±0.1%	59
Example 11	31.4±0.1%	18.3±0.2%	58
Example 12	51.9±0.2%	32.6±0.3%	63
Example 13	37.3±0.1%	20.5±0.2%	55

Example 14	16.3±0.5%	11.8±0.1%	72
Example 15	18.8±0.3%	17.2±1.9%	91
Example 16	33.4±0.9%	10.3±1.6%	31
Example 17	20.3±0.2%	17.5±0.6%	86
Example 18	26.1±1.1%	18.8±0.1%	72
Example 19	35.6±0.4%	15.4±0.7%	43
Example 20	37.8±0.3%	12.7±0.1%	34
Example 21	15.6±0.1%	12.6±0.3%	81
Example 22	39.7±1.2%	14.9±0.4%	38
Example 23	33.1±0.2%	28.1±0.1%	85
Example 24	37.5±0.2%	18.4±0.3%	49

[0118] It can be seen from Table 5 that the ratio ranges from 31% to 93%.

[0119] **VI. Clinical Trial II**

[0120] 1. Patches with the following parameters were obtained by adjusting the preparation method based on the preparation method of the biological patch.

Table 6 Biomechanical Parameters of Examples 25–26

Group	Maximum Tensile Elongation	Elastic strain	Ratio (%)	Single-Suture Tensile Force
Example 25	47.3±0.4%	18.4±0.3%	39	18.2±0.1 N
Example 26	45.4±1.1%	19.8±1.3%	44	22.7±0.9 N

Table 7 Main Differences in Preparation Methods of Examples 25–26

Condition / Group	First Water-Bath Oscillation Condition	Second Water-Bath Oscillation Condition
Example 25	22 °C, 2 h	32 °C, 3.5 h
Example 26	27 °C, 2.5 h	32 °C, 3 h

[0121] Based on Clinical Trial I, 20 additional patients undergoing lung volume reduction surgery were enrolled, and patches from Examples 25 and 26 (10 patients per example, any pulmonary resection site) were used to verify the effect of the ratio on clinical outcomes. The results are shown in Table 8.

Table 8 Results of Clinical Trial II

No.	Group	Air Leakage in Lobectomy	Air Leakage in Wedge Resection	Air Leakage in Bullectomy	No Leakage Total

1	Example 25	2/8	0/2	0/0	2/10
2	Example 26	3/7	1/2	0/1	4/10

[0122] Compared with examples without air leakage in Clinical Trial I, patches from Examples 25 and 26 meet the requirements of maximum tensile elongation, elastic strain, and single-suture tensile force, except that the ratio is lower than 49% (Example 24: 49%). Table 8 further confirms the correlation between the ratio and pulmonary air leakage. Although air leakage was improved in Examples 25 and 26, it is still unacceptable in clinical practice.

[0123] The mechanical properties of the patch must meet the requirements of specific surgical sites. Compared with digestive surgical patches for preventing fluid leakage and bleeding, thoracic surgical patches for preventing air leakage require better elasticity because gas has lower viscosity than liquid. Comprehensive animal experiments and clinical trials show that a biological patch for thoracic surgery with maximum tensile elongation 17.2–51.9%, elastic strain 18.3–39.4%, single-suture tensile force 15.5–33.4 N, and ratio 49–93% has excellent biomechanical properties, ensuring close fitting with lung tissue and preventing pulmonary air leakage.

[0124] In addition, excluding examples unable to be installed on the stapler and those with air leakage in animal experiments and Clinical Trial I, patches from Examples 1, 4–5, 8–13, 16, 18, 23–24 meet thoracic surgery requirements, with parameters: maximum tensile elongation 25.6–51.9%, single-suture tensile force 17.2–33.4 N, elastic strain 18.3–39.4%, ratio 49–93%.

[0125] The preferred embodiments of the present invention have been described in detail above. It should be understood that those skilled in the art can make many modifications and variations based on the concept of the present invention without creative work. Therefore, all technical solutions obtained by logical analysis, reasoning, or limited experiments by those skilled in the art based on the concept of the present invention shall fall within the protection scope defined by the claims.

CLAIMS

What is claimed is:

1. A biological patch for thoracic surgery, characterized in that the biological patch has a maximum tensile elongation greater than 17.2%, an elastic strain greater than 18.3%, and a single-suture tensile force greater than 15.5 N.

2. The biological patch for thoracic surgery according to Claim 1, characterized in that the maximum tensile elongation of the biological patch is 17.2–51.9%.

3. The biological patch for thoracic surgery according to Claim 2, characterized in that the elastic strain of the biological patch ranges from 18.3% to 39.4%.

4. The biological patch for thoracic surgery according to Claim 3, characterized in that the single-suture tensile force of the biological patch is 15.5–33.4 N.

5. The biological patch for thoracic surgery according to Claim 4, characterized in that a ratio of elastic strain to maximum tensile elongation of the biological patch is 49–93%.

6. The biological patch for thoracic surgery according to any one of Claims 1–5, characterized in that the biological patch has a maximum tensile elongation of 25.6–51.9%, a single-suture tensile force of 17.2–33.4 N, an elastic strain of 18.3–39.4%, and a ratio of elastic strain to maximum tensile elongation of 49–93%.

7. The biological patch for thoracic surgery according to any one of Claims 1–6, characterized in that the biological patch for thoracic surgery is made of bovine pericardium.

8. The biological patch for thoracic surgery according to any one of Claims 1–7, characterized in that the biological patch for thoracic surgery is provided with two perforations located at opposite ends of the biological patch.

9. A stapler kit comprising the biological patch for thoracic surgery according to any one of Claims 1–8.

10. A method for preparing the biological patch for thoracic surgery according to any one of Claims 1–7, characterized by comprising:

(1) Pretreatment:

① Immersing healthy bovine pericardial tissue sheets in hypotonic Hank's solution, rinsing repeatedly with fresh hypotonic Hank's solution for multiple times to remove swollen and broken cell debris, nuclei, and organelles after decellularization;

② Rinsing the treated tissue sheets repeatedly with physiological saline for 90–150 min each time, replacing the saline each time, until no visible cells, cellular components, or cell debris are observed under a microscope, and soluble proteins and nucleic acids are undetectable by quantitative determination;

③ Removing phospholipids, non-structural proteins, and part of the tissue matrix from the tissue sheets with a surfactant solution; the surfactant solution may be Tween 80, sodium dodecyl sulfate, or Triton X-100;

④ Soaking in 2.5–4% glutaraldehyde solution for 3–3.5 h;

(2) Chemical modification:

Placing the pretreated tissue material in a chromic hydroxide solution with a Cr^{3+} concentration of 0.0625 mol/dm³ and an OH/Cr ratio of 0.5 for the first water-bath oscillation at 20–28 °C for 2–4 h, adjusting the pH of the treatment solution by 0.3–0.6 units with 10% $NaHCO_3$, followed by a second water-bath oscillation at 32–40 °C for 3–5 h to obtain a single-layer sheet-shaped biological patch.