All animal studies were approved by the School of Medicine Keio University Institutional Animal Care and Use Committee, and were carried out in accordance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institute of Health.

Data are shown as means ± standard deviation. Comparisons were done using Mann–Whitney *U* test (StatView, SAS Institute, Cary, NC). Significance was assumed at $p < 0.05$.

Results

In the pigs, systemic blood pressure, and oxygen saturation remained stable throughout the experiment at approximately 80/50, and 98%, respectively. The probe tip temperature decreased to -135 ± 5 °C within 90 s after initiation of the freeze cycle. The copper plate tip adhered firmly to the pleural surface immediately after the initiation of freezing (Fig. 2A). Pulmonary hemorrhage and edema became macroscopically apparent approximately 5 min after completion of thawing and plate removal (Fig. 2B).

The air leakage pressure was significantly increased in the cryoablation group (40 cmH_2O <) compared to the control group (19 ± 5 cmH_2O) ($p = 0.021$, Mann–Whitney *U* test). Pressure beyond 40 cmH_2O could not be safely applied due to the potential risk of lacerating the membranous portion of the bronchi.

Histologically, cryoablation produced acute pulmonary hemorrhage and edema. The margins were well demarcated. In this experiment, extensive pulmonary hemorrhage reached to a depth of approximately 2 mm (* layer), accompanied by another 2 mm layer of pulmonary edema (** layer) (Fig. 3).

In the long-term experiment in rats, the left lung was used because in rats the left lung usually exist as one lobe, and the experiment was easier to perform. The tip temperature reached −80 °C within 10 s. Air

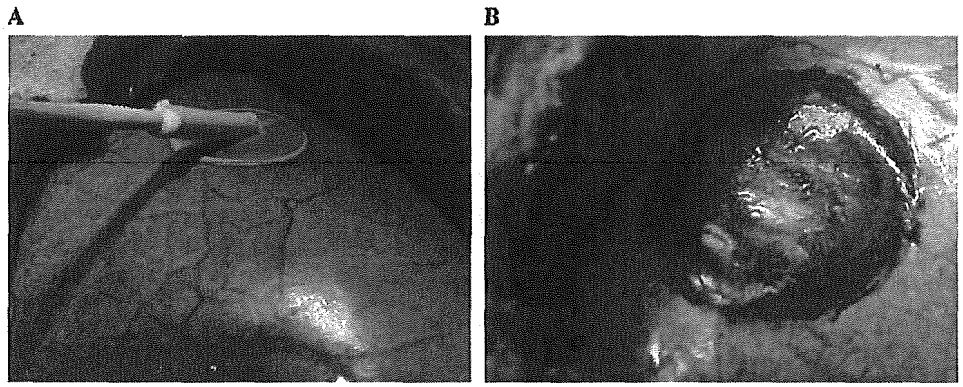


Fig. 2. (A) The copper plate tip adhered firmly to the pleural surface immediately after the initiation of freezing. Frost formation becomes apparent in the frozen area of the pleura. (B) Pulmonary hemorrhage and edema became macroscopically apparent approximately 5 min after thawing.

Fig. 3. Slide glass view of the acute cryolesion in pig lung, H and E staining. Cryoablation produced acute pulmonary hemorrhage and edema. The margins were well demarcated. Extensive pulmonary hemorrhage reached to a depth of approximately 2 mm (* layer), accompanied by another 2 mm layer of pulmonary edema (** layer).

leakage was not apparent after cryoablation at wound closure. All the animals were active, and none died prior to the planned time of sacrifice. The histological finding at 7 h was similar to the acute finding in pigs (Fig. 4A). By 48 h, the lesion progressed to necrosis (Fig. 4B). Inflammatory cell infiltration was prominent at 1 week (Fig. 4C), and by 1 month localized fibrosis was established (Fig. 4D), which remained unchanged up to 2 months that we observed. Normal alveolar structure was present in the surrounding regions of the lung. These changes were consistent with previous reports in animal models using liquid nitrogen probes [8,7].

Discussion

In the present study, in the pigs, experimentally created air leakage from the lung parenchyma was effectively attenuated by superficial cryoablation. The histological studies indicate that in the acute period, this is due to the local obliteration of air spaces as the result of pulmonary hemorrhage. The long-term observations suggest that the layer of acute extensive hemorrhage leads to fibrosis, whereas and the surrounding layer of edema eventually recovers. In rats, we used the ophthalmic cryosurgical device because the freezing capacity of the argon gas probe was far too strong for application in small animals. Although air leakage pressure itself was not measured in the rats, we consider that, as observed in the rats, the fibrotic changes that ensue can effectively prevent air leakage from the cryoablated site in the long-term. We speculate that the extent of the cryolesion, namely the depth, can be controlled by adjusting the freezing time. It has been reported that a stable ice-ball was formed by an argon probe in ex-vivo tissue or warm water bath within 10 min [2]. We chose 5 min of freezing in the present study to ensure sufficient obliteration of the air spaces without excess involvement of the lung parenchyma, but even shorter freezing time may have been adequate. Tissue temperature measurements during cryoablation will be necessary to better predict the extent of the regions of hemorrhage and edema. Using this procedure, we may be able to preserve more lung volume compared to local

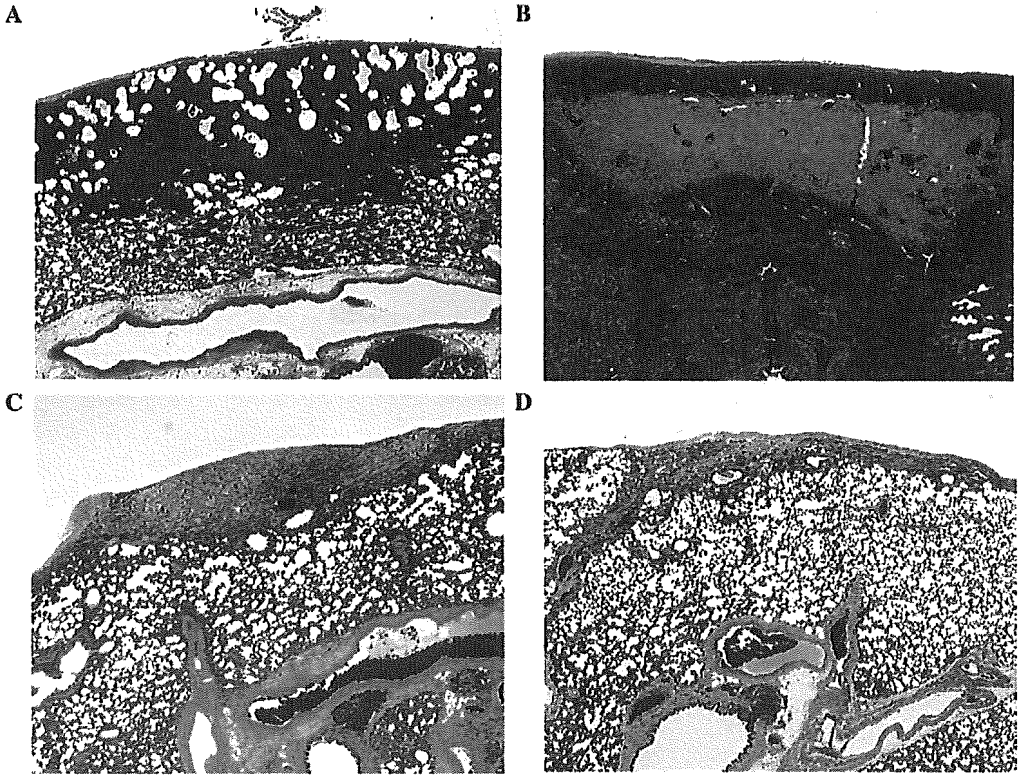


Fig. 4. Histological appearance of the cryolesion in rat lung, H and E staining. (A) The finding at 7 h was similar to the acute finding in the pig, namely extensive pulmonary hemorrhage accompanied by pulmonary edema. (B) By 48, the lesion progressed to necrosis. (C) Inflammatory cell infiltration was prominent at 1 week. (D) By 1 month localized fibrosis was established. The surrounding lung parenchyma appears to be preserved. Magnification 4× in A and B, 2× in C and D.

excision, particularly in cases with broad based bullae. In addition, excess tension to the surrounding pleura, which is speculated to be at least in part responsible for post surgical recurrence of pneumothorax, is less likely to be produced.

Various types of lasers with minimal penetration have been tried to effectively ablate pulmonary bullae [5,6,9,4]. They all have met with moderate success, but their use is still not widely accepted primarily due to the subtle control that is required to avoid the formation of iatrogenic pulmonary fistula. The least invasive, and easy to control of the lasers appear to be the Holmium Yag laser. But even with the Holmium Yag laser, reruptures of bullae are reported and the use of fibrin glue is recommended [4]. Lasers utilize heat. Heat denatures protein and hence can destroy extra cellular matrix (ECM) structures including the pleura when applied excessively. In contrast, freezing primarily damages cells but preserves the ECM and therefore the risk of iatrogenic pulmonary fistula is likely to be less. The thickness of extensive pulmonary hemorrhage by cryoablation was approximately 2 mm in the present study, and far exceeded that of the lesion reported in Holmium Yag laser (less than 0.5 mm) [4]. This suggests that air leakage may be more securely controlled by cryoablation compared to laser irradiation.

The results of this study provide supportive evidence that cryoablation has the potential to stop air leakage from surface pulmonary injury. With more appropriate application of commercially available plate type cryoablation probes, or further improvements in the design of the attachment plate for thoracoscopic use, this procedure may provide a useful adjunct to surgical resection for spontaneous pneumothorax. Another potential application is the control of air leakage from dissected raw lung surfaces during lung resection.

References

[1] J.P. Bonniot, J.P. Homasson, S.L. Roden, M.L. Angebault, P.C. Renault, Pleural and lung cryobiopsies during thoracoscopy, Chest 95 (1989) 492–493.
[2] P.M. Hewitt, J. Zhao, J. Akhter, D.L. Morris, A comparative laboratory study of liquid nitrogen and argon gas cryosurgery systems, Cryobiology 35 (1997) 303–308.
[3] Y. Izumi, T. Oyama, E. Ikeda, M. Kawamura, K. Kobayashi, The acute effects of transthoracic cryoablation on normal lung evaluated in a porcine model, Ann. Thorac. Surg. 79 (2005) 318–322.
[4] S. Kaseda, T. Aoki, N. Hangai, K. Shimizu, H. Kiguchi, One hundred consecutive treatments with holmium: YAG laser for pulmonary bullae: especially in conjunction with gelatin-resorcinol formaldehyde–glutaraldehyde glue adhesion, Lasers Surg. Med. 28 (2001) 255–258.
[5] J. LoCicero 3rd, J.W. Frederiksen, R.S. Hartz, M.W. Kaufman, L.L. Michaelis, Experimental air leaks in lung sealed by low-energy carbon dioxide laser irradiation, Chest 87 (1985) 820–822.
[6] J. LoCicero 3rd, R.S. Hartz, J.W. Frederiksen, L.L. Michaelis, New applications of the laser in pulmonary surgery: hemostasis and sealing of air leaks, Ann. Thorac. Surg. 40 (1985) 546–550.
[7] H.B. Neel 3rd, K.H. Farrell, W.S. Payne, L.W. DeSanto, Cryosurgery of respiratory structures. II. Cryonecrosis of the lung, Laryngoscope 84 (1974) 417–426.
[8] B.M. Rodgers, K.D. Blake, J.A. Alexander, The effects of profound cryotherapy upon the pulmonary parenchyma, J. Thorac. Cardiovasc. Surg. 83 (1982) 784–789.
[9] A. Wakabayashi, M. Brenner, A.F. Wilson, Y. Tadir, M. Berns, Thoracoscopic treatment of spontaneous pneumothorax using carbon dioxide laser, Ann. Thorac. Surg. 50 (1990) 786–789.

ELSEVIER

European Journal of Cardio-thoracic Surgery xx (2005) 1-4

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

www.elsevier.com/locate/ejcts

The sealing effect of fibrin glue against alveolar air leakage evaluated up to 48 h; comparison between different methods of application

Masafumi Kawamura[a,*], Masatoshi Gika[a], Yotaro Izumi[a], Hirohisa Horinouchi[a], Noriko Shinya[b], Makio Mukai[c], Koichi Kobayashi[a]

[a]*Division of General Thoracic Surgery, Department of Surgery, Keio University, School of Medicine, 35 Shinanomachi, Shinjuku-Ku, Tokyo, 160-8582 Japan*
[b]*Pathology Department, The Chemo-Sero-Therapeutic Research Institute, Kumamoto, Japan*
[c]*Division of Clinicopathology, Keio University Hospital, Tokyo, Japan*

Received 4 January 2005; received in revised form 14 February 2005; accepted 15 February 2005

Abstract

Objective: There is little experimental evidence to show how much positive airway pressure fibrin sealants can actually withstand, and in particular, how this effect changes over time. In the present study, we experimentally evaluated the sealing effect of fibrin glue against alveolar air leakage up to 48 h after application. **Methods:** Beagles were used ($n=48$). Under thoracotomy, approximately 5×10 mm defects (2 mm depth) were made on the lung surface. Fibrin glue sealants were applied to this defect in three ways. In rubbing and spray method, fibrinogen was rubbed, followed by spraying of both fibrinogen and thrombin solutions. In double layer method, fibrinogen was dripped, followed by thrombin. Collagen fleece, coated with fibrinogen and thrombin (TachoComb) was also tested. The minimum positive airway pressure which produced air leakage was measured for each sealed defect (seal breaking pressure, cmH_2O) at 0, 3, 6, 12, 24, and 48 h after application ($n=6$ at each time point). **Results:** The seal-breaking pressure increased over time in all of the application methods. At 6 h, differences between methods were not significant but three defects in RS reached 70 cmH_2O, the maximum pressure tested, compared with none in other two methods. At 12 h, the seal-breaking pressure was significantly higher in RS compared with the other two methods (rubbing and spray method vs TachoComb; 66 ± 3 vs 47 ± 17, $P=0.047$, rubbing and spray method vs double layer method; 66 ± 3 vs 42 ± 18, $P=0.024$). Beyond 24 h, sealing pressure reached close to 70 cmH_2O in all the methods. **Conclusions:** The results show that the sealing effect of fibrin glue is relatively unstable up to 12 h after its application. Rubbing and spray method may help the fibrin seal to reach its full strength faster compared with the other two methods.

Keywords: Fibrin glue; Air leakage; Pulmonary resection; Sealing effect

1. Introduction

Alveolar air leakage is a very common complication in lung surgery. Along with inadequate control of postoperative pain, persistence of air leakage was identified as the most common cause of delay in hospital discharge after thoracic surgery [1]. Many tissue sealants are being applied to prevent air leakage after surgery [2-8]. Among them, fibrin glue is a popular sealant with a variety of application methods [9,10]. However, there are also reports that indicate that the use of fibrin glue does not reduce the duration of chest-tube drainage or hospital stay [11-13]. This implies that, air leakage often restarts shortly after surgery despite the application of fibrin glue.

Intraoperatively, we test the efficacy of fibrin glue by applying positive airway pressure. But we usually do not apply pressure beyond 20-25 cmH_2O, since it defeats the purpose to break the seal at this point. Clinically, it is not rare that air leakage becomes apparent, for example through the chest tube, shortly after surgery. While this may be air leakage from lesions that were missed during surgery, it is also true that airway pressure often spikes beyond the pressure tested, 25 cmH_2O, as the patient recovers spontaneous breathing. The fibrin seal may be broken at this point. To our knowledge, there is little experimental evidence to show how much positive airway pressure fibrin sealants can actually withstand, and in particular, how this effect changes over time. In the present study, we experimentally evaluated the sealing effect of fibrin glue against alveolar air leakage up to 48 h after application. We also compared three different methods of application.

2. Materials and methods

2.1. Animals

Adult male beagles, 10-12 months of age, weighing 8-11 kg were used for this study (Toyota Trading Co., Kumamoto, Japan) ($n=36$). Animals were housed individually and provided

* Corresponding author. Tel.: +81 3 5363 3806; fax: +81 3 5363 3499.
E-mail address: kawamura@sc.itc.keio.ac.jp (M. Kawamura).

1010-7940/$ - see front matter © 2005 Published by Elsevier B.V.
doi:10.1016/j.ejcts.2005.02.044

food and water ad libitum. All animal studies were approved by the School of Medicine, Keio University Institutional Animal Care and Use Committee. All animals received humane care in accordance with the Japanese Government Animal Protection and management law

2.2. Fibrin glue application

The fibrin glue used in this study was Bolheal (The Chemo-Sero-Therapeutic Research Institute, Kumamoto, Japan). We also compared, fibrinogen-based collagen fleece, TachoComb (ZLB Behring Co., USA). The mechanism of fibrin glue formation is well described [14]. The fibrin glue product consists of two components. Solution A is a protein concentrate consisting of fibrinogen, plasma fibronectin, factor XIII, and plasminogen, reconstituted in aprotinin solution. Solution B is thrombin reconstituted in calcium chloride solution. TachoComb is a collagen fleece coated with dry fibrinogen and thrombin on one side.

We applied fibrin glue in two different ways, rubbing and spray method and double layer method. In rubbing and spray method, solution A was dripped and gently rubbed onto the air leakage area. Then both solutions were sprayed simultaneously onto the rubbed surface as a mixed aerosol using Bolheal Spray Set (The Chemo-Sero-Therapeutic Research Institute, Kumamoto, Japan). In double-layer method, solution A was dripped onto the air leakage surface after which solution B was dripped. To apply TachoComb, the fibrinogen-coated side was first soaked in saline, and then was attached to the air leakage surface. The sheet was gently pressed with dry gauze for about 5 min so that the collagen fleece was attached to the lung surface with fibrin glue.

2.3. Experiment

The dogs were anesthetized with an intravenous injection of pentobarbital sodium (25-30 mg/kg). The dogs were placed in left decubitus position, intubated, and mechanically ventilated. The right chest wall was shaved, and disinfected. Through a thoracotomy, defects were created on the right lung surface using scalpels, one on each of the three lobes (anterior, middle, and posterior). The defect was created with the lung fully inflated at a positive airway pressure of approximately 20 cmH_2O. The defect size was adjusted to be approximately 5×10 mm, and approximately 2 mm in depth. Hemostasis was obtained when necessary with the minimum use of electrocautery. In each animal, each of the three defects was sealed with one of three methods, rubbing and spray method, double-layer method, or TachoComb. Randomization was performed to allot these three methods to each lobe equally. The chest was closed, and the animals were allowed to recover, except for time 0. Xylazine (2 mg/kg) was administered as needed as analgesics. The minimum positive airway pressure which produced air leakage was measured for each sealed defect (seal-breaking pressure) at 0, 3, 6, 12, 24, and 48 h after the application of the fibrin sealant ($n=6$ at each time point). Except for time 0, thoracotomy was performed again under anesthesia. Air leakage pressure for each defect was evaluated separately by clamping the remaining two lobar bronchi with forceps. The maximum positive airway pressure applied was 70 cmH_2O, since higher pressure induced air leakage from uninjured lung around the hilum. After the completion of seal-breaking pressure measurement at each time point, each animal was sacrificed with intracardiac injections of pentobarbital (1000 mg/body).

2.4. Histological examinations

A separate group of animals was used to obtain histological specimens because the fibrin seal is broken by the seal breaking pressure measurements. Two specimens for each method and time points were prepared ($n=12$). The animals were sacrificed and the whole right lung was fixed in 10% neutral formaline. After fixation, each defect site was resected, embedded in paraffin, and processed in 3 μm sections for hematoxylin-eosin staining. Specimens were analyzed at Clinicopathological Division of Keio University Hospital in a blinded manner by M.M.

2.5. Statistical analyses

The results are presented as the mean ± SD. Seal-breaking pressure per time point was compared between different methods using unpaired *T*-test. Differences within each method were tested using paired *T*-test. Significance was assumed at $P<0.05$.

3. Results

3.1. Seal breaking pressure measurements

The seal-breaking pressure increased over time in all the application methods (Fig. 1). At 0 h, seal-breaking pressure was significantly higher in rubbing and spray method compared with TachoComb (54 ± 5 vs 36 ± 6, $P<0.001$), and in TachoComb significantly higher compared with double layer method (36 ± 6 vs 27 ± 3, $P=0.007$). Seal breaking

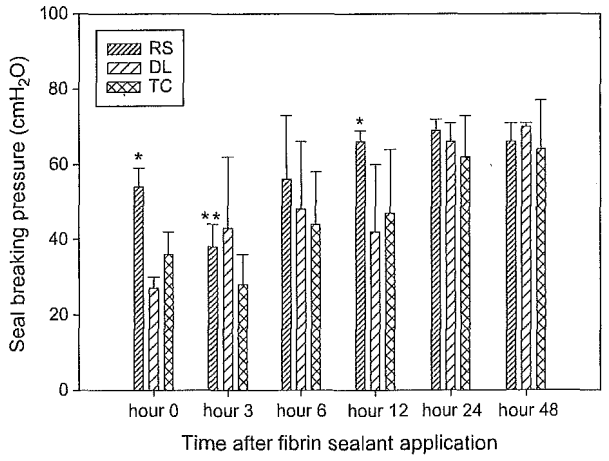


Fig. 1. The time interval changes in seal-breaking pressure after application of the fibrin sealants is shown. RS, rubbing and spraying method; DL, double layer method, TC, TacoComb. *$P<0.05$ vs other two groups, **$P<0.05$ vs RS at 0 h.

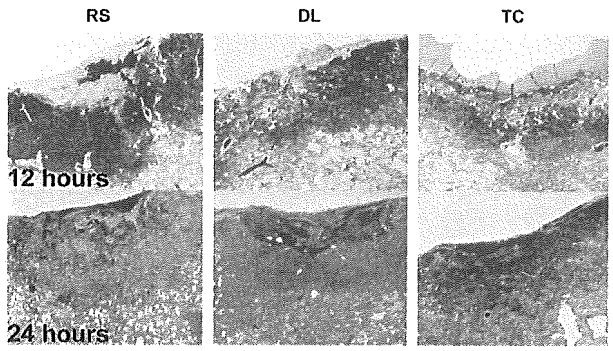


Fig. 2. Hematoxylin-eosin staining of the injured lung sealed by different fibrin sealants. At 12 h, deeper penetration of fibrin into the injured lung parenchyma was seen in RS compared with the other two methods. This difference was not apparent between application methods beyond 24 h. Upper and lower panels correspond, respectively, to 12, and 24 h after sealant application RS, rubbing and spraying method; DL, double layer method; TC, TacoComb, magnification 2×.

pressure in rubbing and spray method declined significantly from 0 to 3 h (from 54±5 to 38±6, $P<0.001$). At 3 h, seal-breaking pressure in double layer method tended to increase, and in TachoComb tended to decline compared with 0 h, but these changes were not significant. At 6 h, differences between methods were not significant but three defects in rubbing and spray method reached 70 cmH_2O, the maximum pressure tested, compared with none in other two methods. At 12 h, the seal-breaking pressure was significantly higher in rubbing and spray method compared with the other two methods (rubbing and spray method vs TachoComb; 66±3 vs 47±17, $P=0.047$, rubbing and spray method vs double layer method; 66±3 vs 42±18, $P=0.024$). Beyond 24 h, sealing pressure reached close to 70 cmH_2O in all the methods, with no significant differences between methods.

3.2. Histological examinations

The layer of fibrin covering the lung surface could be observed in all three methods by hematoxylin-eosin staining (Fig. 2). Up to 12 h, deeper penetration of fibrin into the injured lung parenchyma was seen in rubbing and spray method compared with the other two methods. This difference was not apparent between application methods beyond 24 h. Also, at 3 h, hemorrhage was more evident underneath the fibrin layer in rubbing and spray method compared with other two methods.

4. Discussion

Fibrin glue is derived from human, or in some products like bovine plasma, and hence, carry the same risks as blood transfusion. We have reported the possibility of viral transmission by clinical use of fibrin glue [16]. Despite these potential drawbacks, fibrin glue is widely used in order to reduce postoperative alveolar air leakage, but questions remain regarding its clinical efficacy [5,12,13,15]. The results of this study show that the sealing effect of fibrin glue is relatively unstable up to 12 h after its application. Clinically, this result suggests that coughing or positive pressure ventilation should be kept to a minimum for 12 h in order to fully exploit the sealing effect of fibrin glue.

The sealing effect of fibrin glue is affected by the concentration of fibrin, and how well it attaches to tissue. The concentration of fibrin depends primarily on how well the thrombin and fibrinogen solutions are mixed on application. The attachment of fibrin may be affected at least in part by its penetration into tissue. Rubbing and spray method is a method that we have recently devised. Our intention was to improve tissue penetration by rubbing fibrinogen into the lung parenchyma. We also utilized the effective mixing of the two solutions by aerosol to form a more even layer of fibrin in continuity with the penetrated fibrinogen, which is converted to fibrin by the spray. The present study suggests that rubbing and spray method may help the fibrin seal to reach its full strength faster compared with the other two methods. Histological findings, at least in part suggest that this may be due to the initial deeper penetration of fibrin into the lung parenchyma. We speculate that because of this, the attached surface area of fibrin was initially greater in rubbing and spray method compared with the other two methods. Presumably, this difference became insignificant with the formation of tissue-derived fibrin. We evaluated TachoComb and double layer method as the most widely used methods. Double layer method is the application method recommended by most manufacturers, and is therefore, presumably most often used. It is encouraging that both these methods provided satisfactory sealing effect beyond 24 h. Control experiments, in which no sealant was used, was not performed due to ethical reasons. In our preliminary studies, the alveolar leakage created in this experiment did not stop spontaneously, and respiratory distress was unavoidable even with the use of chest tubes. Regarding rubbing and spray method, there was haemorrhage underneath the fibrin layer at 3 h, which resolved at 6 h. Presumably this was caused by rubbing. This may in part explain the significant decrease in seal-breaking pressure in rubbing and spray method at 3 h. A less invasive way to infiltrate the fibrinogen solution, for instance the use of a soft sponge, is currently being studied.

References

[1] Wright CD, Wain JC, Grillo HC, Moncure AC, Macaluso SM, Mathisen DJ. Pulmonary lobectomy patients care pathway: a model to control cost and maintain quality. Ann Thorac Surg 1997;64:299-302.
[2] Kanno S, Yamazaki H, Kashiwabara S, Uchiyama H, Maekawa Y, Ito G, Muto T, Kariya K, Kojima T, Koshiyama Y, Oda M, Kurumi M. Adhesive and sealing effects of TO-193 on tissues and organs in various experimental models. Folia Pharmacol Jpn 1999;113:269-76.
[3] Otani Y, Tabata Y, Ikada Y. Sealing effect of rapidly curable gelatin-poly (L-glutamic acid) hydrogel glue on lung air leak. Ann Thorac Surg 1999; 67:922-6.
[4] Tsuda T, Nakamura T, Yamamoto Y, Teramachi M, Kiyotani T, Lee YH, Shimizu Y. Prevention of postoperative air leakage from lungs using a purified human collagen membrane—polyglycolic acid sheet. Ann Thorac Surg 1999;68:339-42.
[5] Porte HL, Jany T, Conti M, Gillet PA, Guidat A, Wurtz AJ. Randomized controlled trial of a synthetic sealant for preventing alveolar air leaks after lobectomy. Ann Thorac Surg 2001;71:1618-22.

[6] Ranger WR, Halpin D, Sawhney AS, Lyman M, Locicero J. Pneumostasis of experimental air leaks with a new photopolymerized synthetic tissue sealant. Am Surg 1997;63:788-95.
[7] Macchiarini P, Wain J, Almy S, Dartevelle P. Experimental and clinical evaluation of a new synthetic, absorbable sealant to reduce air leaks in thoracic operations. J Thorac Cardiovasc Surg 1999;117:751-8.
[8] Herget GW, Kassa M, Riede UN, Lu Y, Brethner L, Hasse J. Experimental use of an albumin-glutaraldehyde tissue adhesive for sealing pulmonary parenchyma and bronchial anastomoses. Eur J Cardiothoracic Surg 2001; 19:4-9.
[9] Yuasa K, Shimizu T, Matsubara J, Toyoda T. Sealing effect of fibrin adhesive by various method on protection of air leakage in lung surgery. Kyobu Geka 1998;51:1001-5.
[10] Morikawa T, Katoh H. Improved techniques of applying fibrin glue in lung surgery. Eur Surg Res 1999;31:180-6.
[11] Fleisher AG, Evans KG, Nelems B, Finley RJ. Effect of routine fibrin glue use on the duration of air leaks after lobectomy. Ann Thorac Surg 1990; 49:133-4.
[12] Wong K, Goldstraw P. Effects of fibrin glue in the reduction of postthoracotomy alveolar air leak. Ann Thorac Surg 1997;64: 979-81.
[13] Wain JC, Kaiser LR, Johnstone DW, Yang SC, Wright CD, Freidberg JS, Feins RH, Heitmiller RF, Mathisen DJ, selwyn MR. Trial of a novel synthetic sealant in preventing air leaks after lung resection. Ann Thorac Surg 2001;71:1623-8.
[14] Sierre D. Fibrin sealant adhesive systems: a review of their chemistry, material properties and clinical applications. J Biomater Appl 1993;7: 309-51.
[15] Fleisher AG, Evans KG, Nelems B, Finley RJ. Effect of routine fibrin glue use on the duration of alveolar air leaks after lobectomy. Ann Thorac Surg 1990;49:133-4.
[16] Kawamura M, Sawafuji M, Watanabe M, Horinouchi H, Kobayashi K. Frequency of transmission of human parvovirus B19 infection by fibrin sealant used during thoracic surgery. Ann Thorac Surg 2002;73: 1098-100.

The Acute Effects of Transthoracic Cryoablation on Normal Lung Evaluated in a Porcine Model

Yotaro Izumi, MD, PhD, Takahiko Oyama, MD, Eiji Ikeda, MD, PhD, Masafumi Kawamura, MD, PhD, and Koichi Kobayashi, MD, PhD

Department of Surgery, Division of General Thoracic Surgery, and Department of Pathology, School of Medicine, Keio University, Tokyo, Japan

NEW TECHNOLOGY

Purpose. Percutaneous transthoracic cryoablation of lung parenchymal tumors offers a potentially less invasive alternative to thoracoscopic tumor resection. In the present study, we investigated the feasibility of transthoracic cryoprobe insertion into the lung parenchyma.

Description. Cryoablation was performed in porcine lung through a thoracotomy. A 2-mm diameter cryoprobe was inserted to a depth of 3 cm from the pleura. Cryoablation was performed as one or two cycles of 15-minute freeze followed by 5-minute thaw. Bleeding time and amount, and air leakage pressure from the insertion site was measured and compared between cycles.

Evaluation. The bleeding time and amount significantly increased, and air leakage pressure significantly decreased with two cycles of cryoablation compared with one cycle. Histologically, the primary finding in the cryolesion was localized pulmonary hemorrhage.

Conclusions. Bleeding time, bleeding amount, and air leakage from the insertion site after two cycles (453 ± 202 s, 1.3 ± 0.6 g, and 28 ± 12 cm H_2O, resectively) were considered unlikely to cause acute serious complications. Although long-term studies are needed, the present study provides support for transthoracic cryoablation.

(Ann Thorac Surg 2005;79:318–22)

Cryoablation is currently reestablishing itself as a potential tool in a variety of treatment strategies including multimodality treatment against cancer. This reestablishment is primarily due to advances in the freeze technique and new insights gained in the field of cryobiology [1]. Clinical experience is accumulating regarding organs such as the liver, kidney, prostate, and uterus. There is one clinical report of cryoablation against lung metastasis in which the procedure was performed safely in 112 patients through a thoracotomy [2]. In the lung, percutaneous transthoracic cryoablation of lung parenchymal tumors offers a potentially less invasive alternative to thoracoscopic tumor resection, and moreover, offers potential local tumor control in patients with prohibitive surgical risk. Particularly, with the recent improvements in computed tomography (CT) resolution, and the advent of fluoroscopic CT, we can better plan and maneuver the probe insertion so as to avoid major vessels or airways en route to the tumor. To perform cryoablation percutaneously, however, the possibility of bleeding and air leakage from the lung parenchyma by probe insertion needs to be evaluated. The effects of cryoablation on lung have been evaluated extensively using primarily liquid nitrogen systems [3–5], but in a majority of these studies, the lung was contact frozen through the pleura or bronchus. The objective of this study is to experimentally evaluate the acute effects and feasibility of cryoablation on normal lung when the cryoprobe is inserted into the lung parenchyma through the pleura. This study is also evaluating the effect of cryoablation on the lung using an argon-based cryoprobe.

Material and Methods

Male domestic pigs (weight approximately 40 kg, n = 6) were used for this study. Under general anesthesia, the animals were mechanically ventilated at a respiratory rate of 15 to 20 per minute, tidal volume 10 mL/kg. The airway pressure was sustained at 10 to 15 cm H_2O.

The animals were placed in a left decubitus position and right thoracotomy was performed. Coaxial technique was used for cryoprobe insertion. A stainless steel sheath was inserted into the lung to a depth of 3 cm. This sheath consists of an inner guiding sheath and an external sheath. The external sheath has an inner and outer diameter of 2 mm and 3 mm, respectively. After insertion,

Accepted for publication Sept 10, 2003.

Address reprint requests to Dr Izumi, Division of General Thoracic Surgery, Department of Surgery, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan; e-mail: yotaro@sc.itc.keio.ac.jp.

Published by Elsevier Inc

0003-4975/05/$30.00
doi:10.1016/j.athoracsur.2003.09.082

the inner sheath was removed and a 2-mm diameter cryoprobe (CRYOcare Cryosurgical Unit, Endocare, Irvine, CA) was inserted through the external sheath. The length of the external sheath is 180 mm, equivalent to the length of the cryoprobe, so the cryoprobe tip is located at the sheath tip. The cryoprobe uses high-pressure argon and helium gas for freezing and thawing, respectively, based on the Joule-Thomson principle. Cryoablation was performed as one or two cycles of 15-minute freeze followed by 5-minute thaw. Two cryoprobes were inserted per animal, one each in the upper and lower lobe so as to be well away from each other. The two cryoprobes were allotted to either one or two cycles of cryoablation within each animal. The sheaths and probes were removed together as soon as they acquired mobility during the last thawing.

As indicators for the feasibility of this procedure, bleeding time and bleeding amount from the insertion site and air leakage pressure were measured. Bleeding time was defined as the time from the start of bleeding after sheath removal until its cessation. All the bleeding from the insertion site was carefully absorbed using sponges, which were then weighed to obtain the bleeding amount. After cessation of bleeding, air leakage test was done by progressively increasing positive airway pressure. The positive airway pressure that produced bubbles from each insertion site was recorded as air leakage pressure. These measurements were compared between one and two cycles of cryoablation.

At the end of the experiment, the animals were sacrificed. The right lung was removed and fixed in 10% formalin for hematoxylin and eosin staining. The cryolesion size was evaluated macroscopically on fixed specimen sections and calculated as πr^2 where r is the greatest radius on section. In a separate experiment, two animals were sacrificed 7 hours after two cycles of cryoablation (4 insertions), for hematoxylin and eosin staining, and terminal deoxynucleotidyl transferase-mediated nick end labeling (TUNEL) staining. The TUNEL staining was done using deoxyneucleotidyl transferase (TdT) and biotinylated 2′-deoxyuridine 5′-triphosphate ([dUTP] Roche Applied Science, Indianapolis, IN). Counter staining was done with methyl green. The TUNEL index (%) was calculated as the number of TUNEL-positive cells divided by the total number of stained neuclei. Analysis was done in the center, and periphery of the cryolesion, as well as the surrounding areas of the lung that seemed unaffected on hematoxylin and eosin staining. Five magnification fields, ×400, per area were analyzed in four samples.

All animal studies were approved by the School of Medicine, Keio University, Institutional Animal Care and Use Committee, and were carried out in accordance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institute of Health.

Data are shown as mean ± standard deviation. Comparisons were done using the Mann-Whitney *U* test (StatView, SAS Institute Inc., Cary, NC). Significance was assumed at a p value less than 0.05.

Table 1. The Effects of One or Two Cycles of Cryoablation on Normal Lung

Cryoablation Cycles	One (n = 6)	Two (n = 6)
Cryolesion area (cm^2)	3.3 ± 1.4	10.6 ± 3.4[a]
Bleeding time (sec)	204 ± 85	453 ± 202[a]
Bleeding amount (g)	0.5 ± 0.3	1.3 ± 0.6[a]
Air leakage pressure (mm H_2O)	48 ± 13	28 ± 12[a]

[a] $p < 0.05$ versus one cycle, Mann-Whitney *U* test.

Results

Systemic blood pressure and oxygen saturation remained stable throughout the experiment at approximately 80/50 and 98%, respectively. The probe tip temperature decreased to −135 ± 5°C within 90 seconds after initiation of the freeze cycle.

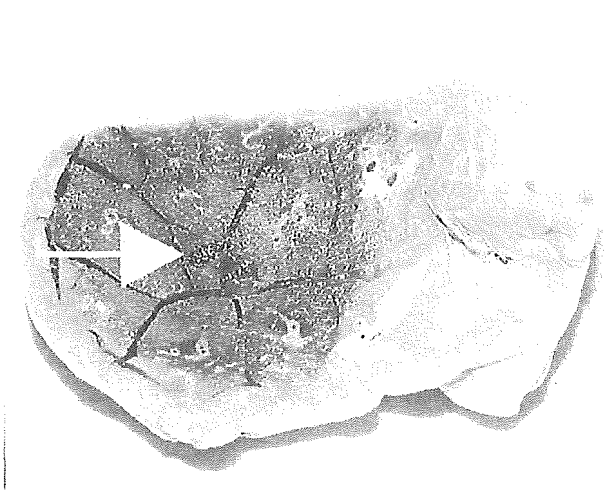
The lesion area tripled with two cycles of cryoablation versus one cycle. The bleeding time and amount significantly increased with two cycles of cryoablation versus one cycle. The air leakage pressure significantly decreased with two cycles of cryoablation versus one cycle (Table 1).

Macroscopically the cryolesion appeared as a well-defined hemorrhagic region (Fig 1, A). The insertion site is visible in the center of the lesion (Fig 1, A, arrow). Note the cracks formed by cryoablation along the margins and inside the cryolesion. Microscopically, the cracks were demonstrated to represent widening of the interlobular septa, which formed a relatively clear demarcation of the cryolesion (Fig 1, B). The primary finding in the cryolesion was severe localized pulmonary hemorrhage (Fig 1, C). The vessel and airway structures were difficult to identify, and necrosis was considered to be inevitable although the neuclei were still intact at this point. Large vessel and airway structures were conserved toward the periphery of the cryolesion (Fig 1, D). These findings were similar at 7 hours after cryoablation. At that time, TUNEL staining revealed TUNEL-positive cells primarily in the periphery of the cryolesion (Fig 1, E), none in the center, and a very small number in the areas adjacent to the cryolesion, which seemed unaffected on hematoxylin and eosin staining (Fig 1, F). The TUNEL index was as follows: periphery 0.6% ± 0.3% ($p < 0.05$ versus center and unaffected area, Mann-Whitney *U* test), center, 0%; and unaffected area, 0.1% ± 0.1%.

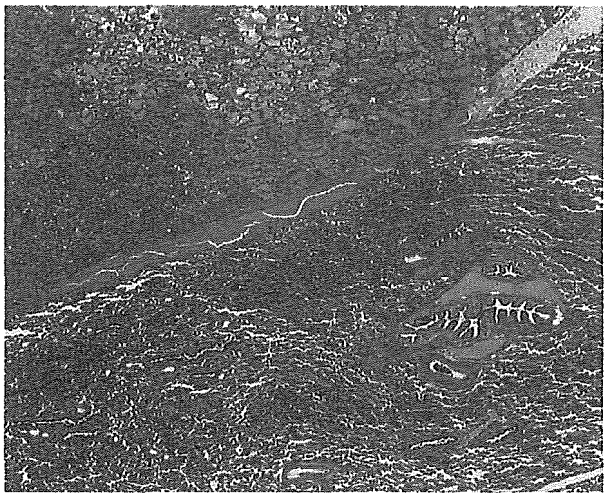
Comment

In the present study, we performed one or two cycles of cryoablation primarily to simulate cancer treatment that we would anticipate applying in the future with this procedure. Although multiple freeze-thaw cycles are recommended for cancer treatment, at the same time it is reported that one cycle may be sufficient at significantly low temperatures [1]. Also, it has been reported that a stable ice-ball was formed by an argon probe in ex-vivo tissue or warm water bath within 10 minutes [6]. So we

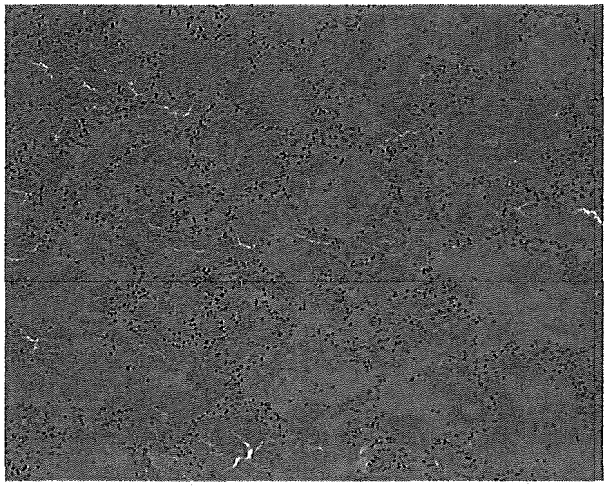
Ann Thorac Surg
2005;79:318–22



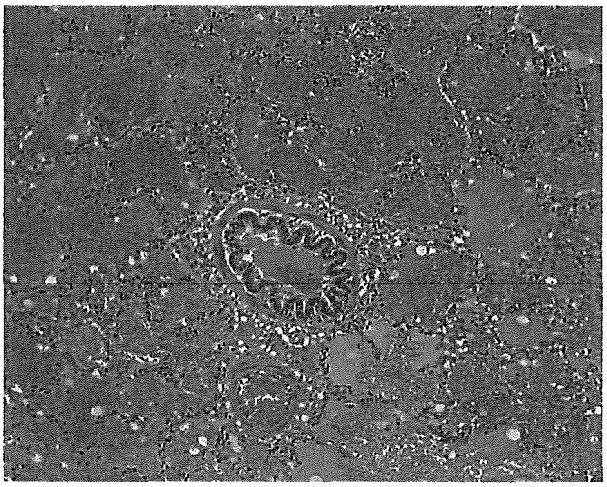
A



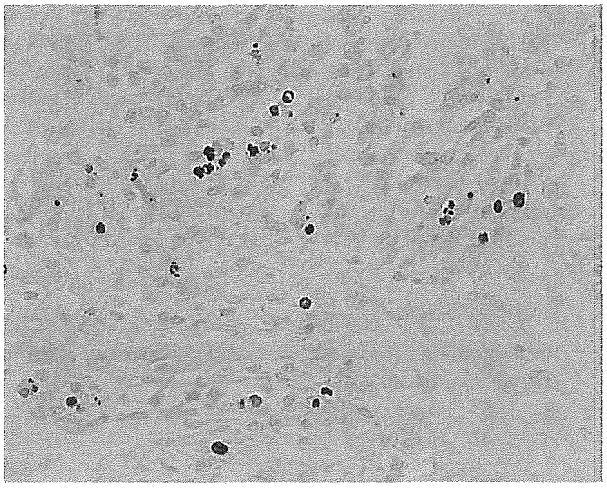
B



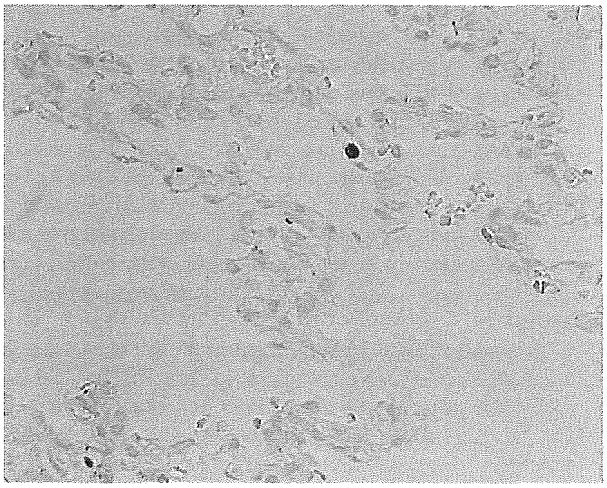
C



D



E



F

Fig 1. (A) On fixed specimen, the cryolesion appeared as an area of well-circumscribed hemorrhage around the probe insertion site (arrow). Cracks due to cryoablation could be seen at the margin and inside the cryolesion. (B) Microscopically, the cryolesion was demarcated by widened interlobular septa (hematoxylin & eosin staining, ×5). (C) There was severe localized pulmonary hemorrhage in the cryolesion. The vessel and airway structures were difficult to identify, and necrosis was considered to be inevitable although the neuclei were still intact at this point (hematoxylin & eosin staining, ×20). (D) In the periphery of the cryolesion, intact vessel and airway structures could be seen (hematoxylin & eosin staining, ×20). (E) Terminal deoxynucleotidyl transferase-mediated nick end labeling (TUNEL) positive cells were observed primarily in the periphery of the cryolesion (TUNEL staining, ×40). (F) Scattered TUNEL-positive cells were present in the areas adjacent to the cryolesion that seemed unaffected on hematoxylin & eosin staining (TUNEL staining, ×40).

considered up to two cycles of 15 minutes of freezing to be adequate in order to test the feasibility of this procedure.

It is interesting that the lesion area significantly enlarged after the second ablation. We speculate that this is because the lung consists mostly from air spaces, and that the freezing property of the lung likely changed after the first cycle due to the extensive pulmonary fluid obliterating the air spaces [7]. Although bleeding increased and air leakage pressure decreased after two cycles of cryoablation compared with one cycle, data after two cycles of cryoablation still suggest that transthoracic cryoablation in the lung parenchyma is unlikely to cause serious acute complications such as extensive pneumothorax, hemothorax requiring drainage, or massive airway bleeding. Survival studies are necessary to address the effects over a longer time course.

Findings on hematoxylin and eosin staining showed that the acute effect of cryoablation on the lung is pulmonary hemorrhage with destruction of vessel and airway structures, particularly in the center of the cryolesion. It is conceivable that this local effect contributed to the control of bleeding and air leakage from the probe insertion site after the procedure. Toward the periphery of the cryolesion, large vessels and airways were preserved. We speculate that flow of blood or air, if above a certain range, prevents the cooling of vessels or airways. These acute changes were still present 7 hours after cryoablation. These findings were very similar to previous reports using liquid nitrogen probes [3–5], suggesting that the slightly faster freeze rate of an argon probe [6] did not affect the outcome significantly.

We found presence of TUNEL-positive cells primarily in the periphery of the cryolesion. This finding is consistent with previous in vitro studies showing induction of apoptosis at sublethal level of cryoinjury [8], although that has not been previously documented in vivo. Very few TUNEL-positive cells were observed in the region that seemed unaffected on hematoxylin and eosin staining. This suggests that hematoxylin and eosin findings adequately reflect the interim extent of the cryolesion although further studies are necessary to address long-term effects.

Radiofrequency ablation is another modality to obtain local tumor control without resection. The effects of radiofrequency ablation on lung has been studied in an animal model, and the histologic changes seem to be very similar to our findings [9]. The lung is unique in that air is contained within the structure, and it is reported that presumably less thermal energy is deposited in lung tissue compared with solid organs due to increased impedance [9]. The formation of fluid during either procedure, which obliterates the air space, most likely alters energy conductivity whether it be heat or cold. Indeed, in the present study, the lesion area tripled after two cycles of cryoablation compared with one cycle. Comparison under the same experimental condition is necessary to determine if there are differences in the mechanism, and outcome of lung injury caused by excessive heat or cold.

In the clinical setting, the extent of the cryolesion should likely be evaluated or predicted during the cryoablation procedure by real-time imaging, most likely CT in the case of lung. Therefore, the correlation between histologic and radiologic findings needs to be investigated. Also needing to be accounted for is that the properties of the tumor will significantly alter the way in which the surrounding lung is affected when this procedure is applied to the treatment of lung tumors [10].

Disclosures and Freedom of Investigation

The Endocare cryoprobes and cryoablation apparatus were purchased by the School of Medicine, Keio University. The authors have performed a free and independent evaluation of this technology. None of the authors has any financial relationship with Endocare.

References

1. Gage AA, Baust J. Mechanisms of tissue injury in cryosurgery. Cryobiology 1998;37:171–86.
2. Xiang J, Xie D, Qiu J. Cryosurgical resection of pulmonary metastases (experience of twenty years). Zhonghua Wai Ke Za Zhi 1995;33:639–40.
3. Neel HB III, Farrell KH, Payne WS, DeSanto LW. Cryosurgery of respiratory structures. II. Cryonecrosis of the lung. Laryngoscope 1974;84:417–26.
4. Rodgers BM, Blake KD, Alexander JA. The effects of profound cryotherapy upon the pulmonary parenchyma. J Thorac Cardiovasc Surg 1982;83:784–9.
5. Gorenstein A, Neel HB III, Sanderson DR. Transbronchoscopic cryosurgery of respiratory structures: experimental and clinical studies. Ann Otol Rhinol Laryngol 1976;85:670–8.
6. Hewitt PM, Zhao J, Akhter J, Morris DL. A comparative laboratory study of liquid nitrogen and argon gas cryosurgery systems. Cryobiology 1997;35:303–8.
7. Lee CY, Bastacky J. Comparative mathematical analyses of freezing in lung and solid tissue. Cryobiology 1995;32:299–305.
8. Hoffmann NE, Bischof JC. The cryobiology of cryosurgical injury. Urology 2002;60:40–9.

Ann Thorac Surg
2005;79:318–22

9. Goldberg SN, Gazelle GS, Compton CC, McLoud TC. Radiofrequency tissue ablation in the rabbit lung: efficacy and complications. Acad Radiol 1995;2:776–84.
10. Bischof JC, Bastacky J, Rubinsky B. An analytical study of cryosurgery in the lung. J Biomech Eng 1992;114:467–72.

Disclaimer

The Society of Thoracic Surgeons, the Southern Thoracic Surgical Association, and *The Annals of Thoracic Surgery* neither endorse nor discourage use of the new technology described in this article.

INVITED COMMENTARY

This straightforward study demonstrates that in an acute porcine model, transpleural pulmonary cryoablation (cryo) with an argon-based device creates significant tissue necrosis (and apoptosis) without a degree air leak or blood loss that is likely to result in major complications. Although pulmonary cryo is not new (note the referenced Chinese clinical study), this work is timely because of the recent interest in radiofrequency ablation (RFA) for pulmonary tumors. If cryo is demonstrated to be equally safe and effective in comparison to RFA, it may provide an alternative mode of localized ablation of lung tumors in poor operative candidates.

Chief among the admitted weaknesses of this study is that the ablation was done on normal lung tissue. Certainly, the gross and histological effects of cryo will be different in tumor tissue. Second, the study is an acute one, with animals (in the main group) sacrificed only a few minutes after cryo. Although the bleeding amount and air leakage pressures do seem within a safe range, only a survival study can confirm that there is not a risk of hemothorax or prolonged air leak. Furthermore, this study does little to dispel our concerns regarding the risk of major hemorrhage following such nonresective, ablative therapies, since the cryo is taken here to a depth of only 3 cm where major vessels are not found.

It should be mentioned that in the liver, cryo has been largely abandoned in favor of RFA for a variety of reasons. These include an apparently increased risk of hemorrhage with cryo and an incompletely explained postcryo, systemic inflammatory response syndrome. Newer generation, argon-based cryo devices as used in this study may or may not impact these problems, and they may or may not be issues when the lung is the target organ. Finally, one must consider an important concern with this work that is common to the potential clinical application of any nonresective ablative therapy. This is the concern that if these therapies begin to be applied by individuals without a deep knowledge of thoracic oncology, that they may be applied inappropriately. Such technologies will find appropriate application only in very unusual clinical scenarios. To assure that they are applied only in these instances, it is critical that thoracic surgeons remain at the forefront of their development.

Joseph B. Shrager, MD

Department of Surgery
Hospital of the University of Pennsylvania
4th Floor Silverstein
3400 Spruce St
Philadelphia, PA 19104-4283
e-mail: jshrag@mail.med.upenn.edu

0003-4975/05/$30.00
doi:10.1016/j.athoracsur.2003.11.009

心臓外科

Knack & Pitfalls

弁膜症外科の要点と盲点

監修▶高本眞一［東京大学教授］
編集▶四津良平［慶應義塾大学教授］

文光堂

2. Ross手術：自己肺動脈弁を用いた大動脈弁置換術

饗庭 了

[慶應義塾大学医学部外科（心臓血管）]

はじめに

Ross手術はautograft（自己肺動脈弁）を用いた大動脈弁置換手術であり，1967年Donald Rossが報告した方法である[1]．大動脈弁置換手術のうちで唯一，生きている弁を用いる手術である．したがって，人工弁の植込み後に生じうる，弁stuck，血栓塞栓症，出血，溶血，感染などの重篤な合併症がなく，またその弁の血行動態上の性能はあらゆる人工弁を上回り，また小児では弁構造の成長が見込めるという数々の利点を持っている．一方で，手術手技が複雑になることに伴う術後早期リスク，弁機能の耐久性，autograft基部の遠隔期の拡張，肺動脈弁位に植え込んだ代用弁の耐久性（ただし閉鎖不全は長期に耐えうる）といった数々の懸念がある．したがってその適応を決定する際にはこれらの功罪を考慮に入れて対処すべきである．現在，Ross手術の適応に関しては，積極的に小児から50歳以上までの幅広い年齢，背景疾患を対象とするElkins[2]や10歳代の若者を含め可及的に行わない方針としているとするJonas[3]まで専門家間で意見が大きく分かれている．しかし，小児の大動脈弁置換においては本術式が第一の適応となる．以前はKonno手術などの人工弁を用いた弁輪拡大術が多く行われたが，現在ではRoss手術が行われることが多くなった．新生児乳児においても適応となる場合がある．ワルファリン服用が不要なため，妊娠可能年齢の女性や，運動家などの活動性の高い患者がよい適応である．また感染性心内膜炎による大動脈弁疾患にも適応が存在する．

1. 手術手技

胸骨正中切開にて心臓に到達し，遠位上行大動脈送血，上下大静脈脱血によって完全体外循環を確立する．

まず，心拍動下で，autograftの採取を開始する．主肺動脈を最も遠位部すなわち左右分枝肺動脈との接合部で横切断することにより主肺動脈壁のすべてをautograft側につけて採取する．なぜなら主肺動脈の長さは個体差がありこれが短いケースでは前側の交連を手術などで構造物が癒着している場合などは左右分枝肺動脈との接合部に最初に目印をつけておくとよい．

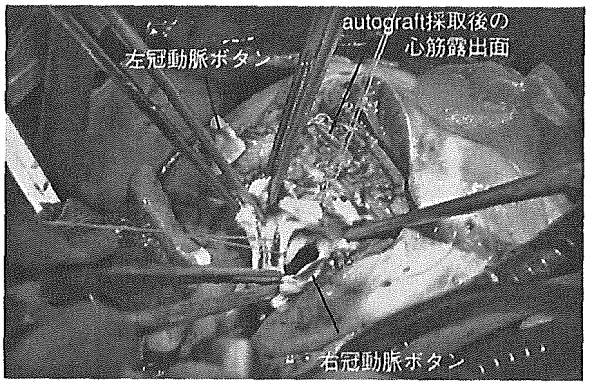
著者らは，この時点で心停止を導入する．上行大動脈を遮断し，心筋保護液を順行性に注入する．右室流出路の横切開の時には，切断した主肺動脈から肺動脈弁輪を確認し，直角鉗子を入れて弁輪の最下部から正確に2～3mmのレベルで始める．心室中隔の切開では左冠動脈の損傷しないように十分に留意する．左前下行枝はautograftの後側を走行しているが，再手術による癒着などで左前下行枝が視認しづらい時には，大動脈をST接合部よりやや遠位で横切断し，左冠動脈口からプローベを左前下行枝に挿入してこれを心外膜側より触知する．第一中隔枝は三尖弁の内側乳頭筋基部を通る横隔膜からの垂線に一致して位置している[4]．心室中隔は右室側から見て第1層と第2層の間を切離していく．筋束走行が変化する深さが筋層間であり，この切開線のうち大動脈と肺動

脈との接合部でのみ線維弁輪骨格を切離する．

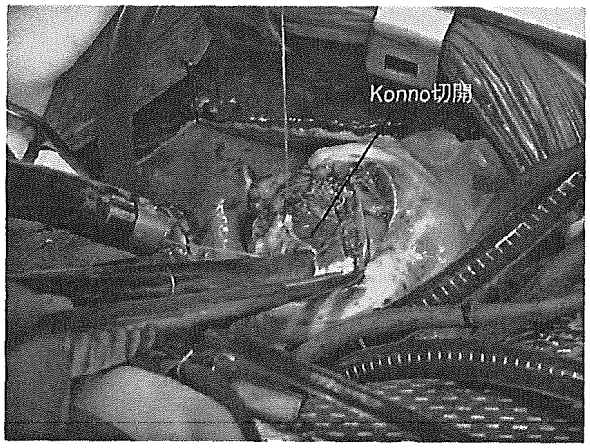
大動脈弁の狭小弁輪のためにRoss-Konno手術を行う時には右室自由壁をU字型に切開しこの部分がautograft側に付着するようにする．採取したautograftは生理食塩水を満たして，弁の接合を確認し，弁輪のサイズをHegar dilatorで測定した後，心嚢内でice slushを用いて保存しておく．

autograftの植込み術式は，基部置換法，subcoronary法，シリンダー内挿法などがあるが，2005年現在，最も普及していると思われる基部置換法について述べる．

左右の冠動脈ボタンを大きめのカフをつけて作成しておく．続いて大動脈弁尖を切除する（図1）．そして大動脈弁輪のサイズをHegar dilatorで測定する．前に測定したautograftのサイズと±2 mm程度の差であれば弁輪径の調整手技は必要ない．弁輪径を拡大する時には，左冠尖-右冠尖間の交連部で心室中隔を切開するKonno切開（図2）を加える（Ross-Konno手術）．また弁輪径を縮小する時には，弁輪外周に（目標弁輪外径×π）の長さのdacron felt帯を縫着する（annulus reduction）．また，成人においては弁輪径の調整が不要な場合であっても，遠隔期の弁輪拡張を予防する意味で弁輪外周の長さのdacron felt帯を縫着する（annulus fixation）．まず第1列の針糸のうち，autograft弁輪最下部（nadir）3点を対応する大動脈弁輪にかける．この時，大動脈弁は必ずしも120°対称となっていないことがあるので，大動脈弁輪にかける位置を調整して，autograftが歪まないように留意する．autograftはRoss手術の場合は120°反時計回りに回転させてautograft前尖（右室流出路との連続部分）を無冠尖部分になるようにし，Ross-Konno手術の場合は回転させずにautograft前尖と右室流出路の延長部分がKonno切開にはまるように位置させる（図3）．大動脈弁輪に対してscallopではなくできるだけ円形となるように交連部では左室内膜面にかける．dacron felt帯を縫着する時にはこの針糸を巻き込むようにかけていく．この時，



［図1］autograft採取，大動脈弁切除，と左右冠動脈ボタンの作成



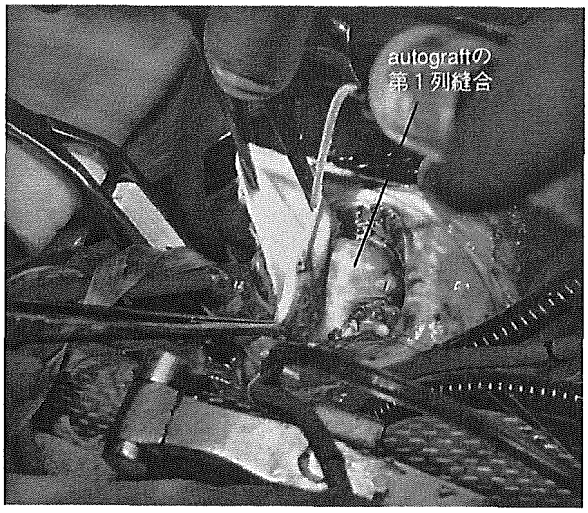
［図2］Konno切開による弁輪拡大

autograftをいったん左室内にinvertすると視野が改善することがある．次に左冠動脈を再建する．autograftのValsalva洞内に冠動脈ボタンより小さい孔をあけて，冠動脈ボタンを縫合する．続いて上行大動脈-autograft吻合を行う．上行大動脈が拡大している時には人工血管置換や大動脈壁縫縮を追加するが，autograft側は切り込みを入れないようにする．最後に右冠動脈ボタンの吻合する正確な位置を決定して左冠動脈と同様の方法で再建する．

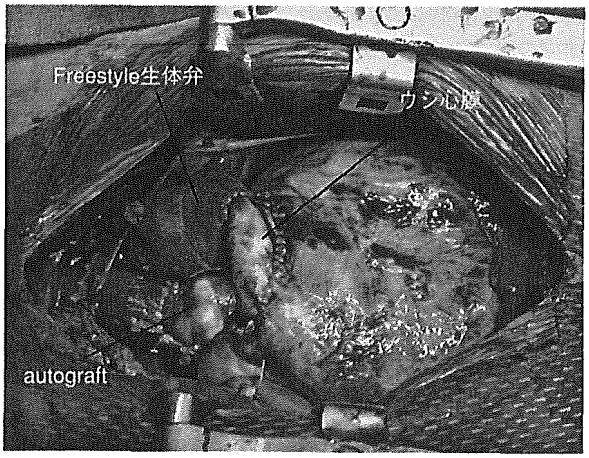
続いて右室流出路の再建に移る．最適の材料はpulmonary valved homograftであるが，本邦においては入手が困難であり，他の材料を用いざるを得ないことが多い．著者らは主としてMedtronic Freestyle異種生体弁を用いている．

◎autograft 採取の際，左冠動脈の損傷を避ける．
◎基部置換法では第1列の針糸は scallop 型ではなく円形に配列するようにかける．
◎homograft が入手できない場合でも右室流出路再建には異種生体弁などで対応が可能である．

まず心停止の間に autograft を採取した後の心室中隔の断端は心内膜の欠如した心筋組織露出面であり，左冠動脈または第一中隔枝からの小枝からの出血を予防するために心筋保護液を注入して，電気メスなどで十分に止血しておく．homograft が入手できる場合には右室心内膜と直接縫合しても，内膜組織の裂開が生じることはない．Medtronic Freestyle 異種生体弁を含めて，他の材料では柔軟性に問題があるので，まず心筋組織露出面全体を自己心膜で覆って閉鎖しておき，この自己心膜に生体弁を縫合する．右室の中隔側との吻合が終了して大動脈の遮断を解除する．心拍動の再開を確認した後，右室前壁の縫合を行う．Ross-Konno 手術を行った時には，ここにさらに異種心膜などの補塡を必要とすることが多い．主肺動脈と吻合の端々吻合を行って，心内操作を完了する（図4）．



[図3] autograft の基部置換法による植込み操作（第1列終了）



[図4] Ross-Konno 手術の完成図

おわりに

最近の動向として，大動脈弁閉鎖不全に対しての適応を慎重に考える意見が増えていることと，autograft の植込み方法も遠隔期の autograft 拡張を防止する観点から，Ross 原法の subcoronary 法やシリンダー内挿法が復活していることがあげられる．

文献
1) Ross, DN : Replacement of aortic and mitral valves with a pulmonary autograft. Lancet 2 : 956, 1967
2) Elkins, RC : The Ross operation : a 12-year experience. Ann Thorac Surg 68 (3 suppl) : S14-18, 1999
3) Jonas, RA : The Ross procedure is not the procedure of choice for the teenager requiring aortic valve replacement. Semin Thorac Cardiovasc Surg Pediatr Card Surg Ann 8 : 176-180, 2005
4) Hosseinpour, AR, Anderson, RH, Ho, SY : The anatomy of the septal perforating arteries in normal and congenitally malformed hearts. J Thorac Cardiovasc Surg 121 : 1046-1052, 2001

6 修正大血管転位症

修正大血管転位症（congenitally corrected transposition of the great arteries）とは，解剖学的な接合関係が右房－左室－肺動脈，左房－右室－大動脈である先天性心奇形と定義される。内臓心房位が正位と逆位の場合があり，98% 以上の例で合併心内病変が存在する。

手術適応となることの多い病変は，心室中隔欠損，肺動脈狭窄，三尖弁（左側房室弁）閉鎖不全，機能的単心室の4つであり[1]，また高度房室伝導障害の発生頻度も高い。生命予後はこれらに加え，解剖学的右室の機能不全の有無と程度が関与する[2]。

特に，三尖弁（左側房室弁）閉鎖不全，高度房室伝導障害，右室機能不全はその発生時期が症例によりばらつきが大きく，また相互に悪化させる因子として作用するので，手術時期の選択はこの3つの因子によって決定されることが多い。

現在，機能的または解剖学的修復術には，conventional repair，anatomical repair（double-switch），1 + 1/2心室修復，modified Fontanなどの選択肢があり，その選択基準は個々の解剖学的，機能的な多因子によってまた施設の経験によって決定される。

A. 手術方法

1. conventional repair

この術式では合併する病変に対する修復のみを行う。手術術式はanatomical repairに比較してよりsimpleであり，手術手技として低侵襲であるといえる。また心房や心室内の縫合線も少なく，これに起因もしくは関連する遠隔期不整脈の発生頻度が少ないことが期待される。しかしながら，解剖学的接合関係の異常は放置するので，修復術後も解剖学的右室や三尖弁が術前と同様に体血圧に曝される。これらの構造物の機能が長期遠隔期に低下する懸念がある。歴史的にも1957年以降[3] anatomical repairが発表される1990年までの中心的存在であった。これらの比較的古い時代に報告されたconventional repair後の長期成績はFontan手術後のものと同様にmortality，morbidityともに二相性の曲線を描いて上昇する[4]。この不満足な遠隔成績がanatomical repairの開発の推進力になった。ただし，筆者の経験では1990年以降に手術を行ったconventional repairの中期遠隔成績はそれ以前のものと比較して有意に改善し（図6-55），同時期のanatomical repairを行った他施設の成績[5]と同等かそれ以上に良好であり，両者の優劣の判定には更に長期の経過観察による比較を必要とする。以下にこれらの病変に対する修復術式について述べる。

a. 心室中隔欠損（ventricular septal defect：VSD）

VSDが存在する場合は血行動態的にunrestrictiveなサイズがあり，inletよりに位置する。

本疾患の外科治療では，特に房室伝導系の解剖的知識が最重要である[6]。原則として，房室結節は前方と後方の2個存在し，心房中隔と心室中隔のalignmentがずれている本疾患の特徴によって，

心室中隔との距離がより短いほうの房室結節のみがより下位の伝導系組織（His束）と接続し，伝導系として機能する。この原則に基づいて内臓心房位が正位の場合には前方房室結節が機能することが多くなり，心房中隔の前方limbusが右側房室弁弁輪に達した地点に位置する。これよりHis束は線維三角を貫き肺動脈弁弁輪の前方をまわってVSD辺縁に達しその上前縁を下降していく。内臓心房位が逆位の場合には心房中隔と心室中隔のalignmentが症例により大きく異なるため機能する房室結節は前方のことも後方のこともある。また，両方の結節と心室中隔との距離が近似している場合，両方の結節がそれぞれHis束を従えVSD辺縁でslingを形成し，頻拍性不整脈の原因となることがある。

パッチ縫着の到達法は従来多くの方法が提唱されたが現在ではconcordant heartと同様に経右房，経右側房室弁（僧帽弁）が最も一般的である（図6-56）。VSDの前下縁ではVSDごしに解剖学的右室側の心室中隔に針糸をかけパッチを組織に固定して，残りの部分の運針を解剖学的左室側より進める[7]。His束の位置はVSD辺縁の解剖学的左室側で青白い筋としてしばしば視認可能である。またVSDごしに三尖弁（左側房室弁）内側乳頭筋の付着部位を確認することが重要で，たとえ軽度のstraddling（内側乳頭筋がVSDの辺縁に付着している）であっても，刺激伝導系と三尖弁（左側房

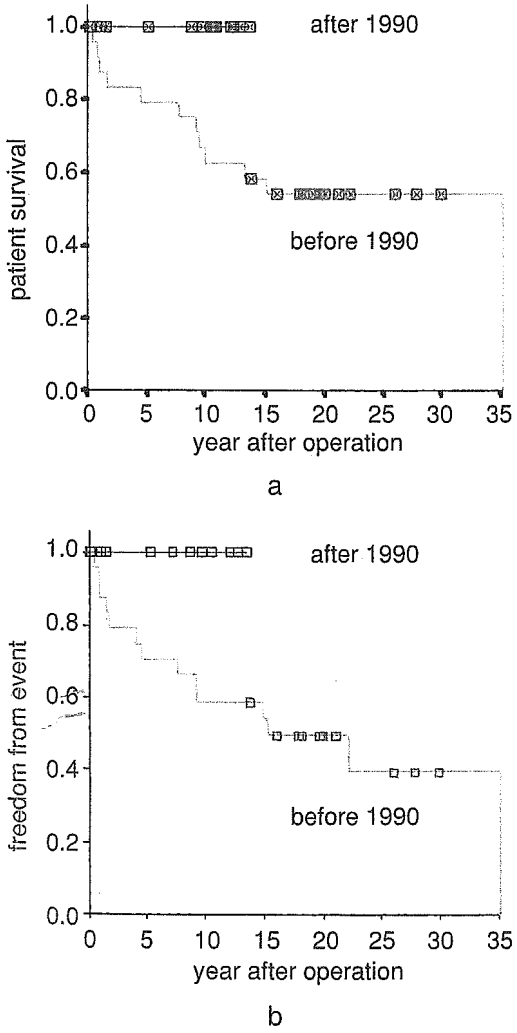


図6-55　conventional repairの年代別成績
（慶應義塾大学病院）

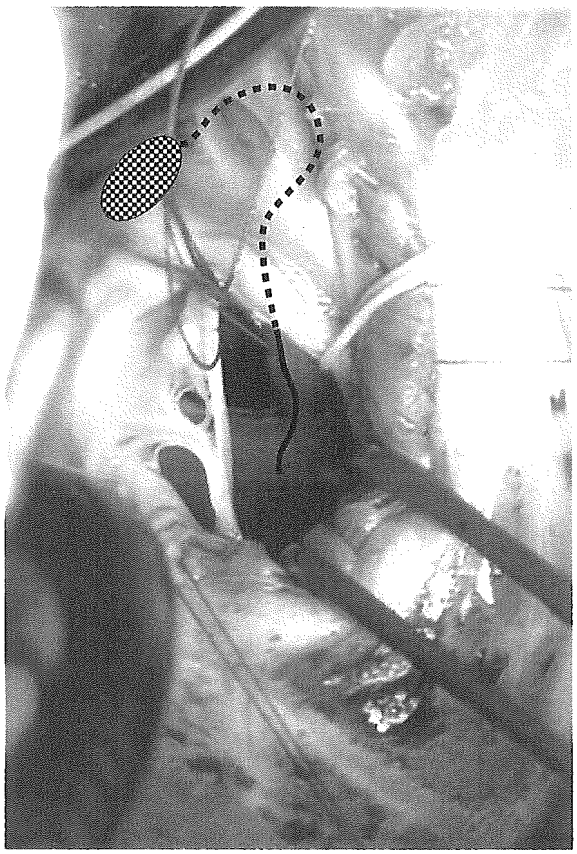


図6-56　VSDへの経僧帽弁到達と房室伝導系損傷を回避する縫合糸の置き方
頭側が上。房室結節と左側His束の位置の想像図

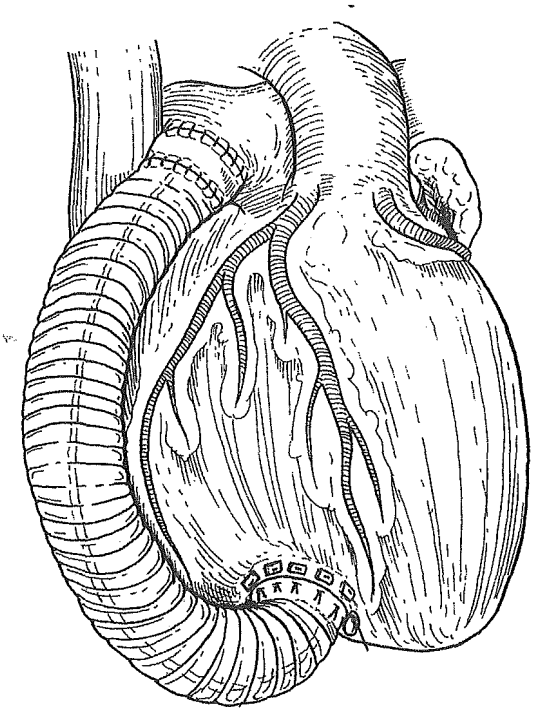


図6-57　Rastelli型conventional repairの心外導管の置き方

室弁）内側乳頭筋の両方の機能を温存することは困難であるためanatomical repairなど他の術式を考慮すべきである。

b. VSDおよび肺動脈狭窄

この解剖学的組み合わせでは，狭窄が軽度でない限りチアノーゼを呈する。体肺動脈シャント術の適応となることがあるが，この場合解剖学的右室に容量負荷がかかり，三尖弁閉鎖不全を伴って心不全を招くリスクがあることに留意すべきである。肺動脈狭窄部位は弁下部と弁輪低形成，弁尖の可動性低下，およびそれらの組み合わせである。狭窄解除の術式として以下のものから狭窄度や解剖学的左室－肺動脈空間的位置関係に応じて選択する。なお，過度の狭窄解除は解剖学的左室の機能障害とともに心室中隔の左室側への偏位に伴う三尖弁内側乳頭筋の偏位によって生じる三尖弁閉鎖不全の発生を招きむしろ有害である。

交連切開術は，狭窄が弁尖の可動性の低下のみにより起因している場合に選択する。中等度以下の弁閉鎖不全を生じてでも狭窄解除が有効な場合この術式を選択する。

パッチ拡大術は，弁輪径が軽度ないし中等度に小さい場合に適応となる。解剖学的左室流出路－肺動脈弁輪切開線は右側（解剖学的左）冠動脈を避けて背側に置く方法と解剖学的左前下行枝と房室間溝の間に置く方法がある。concordant heartの場合の右室流出路パッチ形成術（Fallot四徴症修復術など）と比較して，本疾患においては左室漏斗部が欠落または低形成となっているので有効な狭窄解除が可能となる症例は比較的限定される。

心外導管による修復術（Rastelli型手術）は最も頻繁に用いられる狭窄解除法である。冠動脈走行の形式により解剖学的左室流出路切開が不能な場合などに適応がある。筆者[8]は左室心尖部に（心尖部よりではなく）心室切開を置く術式を提唱している（図6-57）。心室切開を置く前に心室の内側から指で僧帽弁乳頭筋の付着部を確認し，これを避けて切開することが肝要である。この方法では胸骨との接触を避けて必然的に心外導管は長くかつ彎曲したものになるが，そのために導管の寿

命が限定されることはない。

c. 三尖弁(左側房室弁)閉鎖不全

左側房室弁は形態的にはconcordant心の三尖弁と相同であることが多いが，例外も少なくない。弁尖の変性や腱索の肥厚がしばしばみられる。一般にEbstein様変化という表現が使われることがあるが，その意味はEbstein奇形の三尖弁と共通するのは後尖と前尖の一部の弁輪が心尖部側に偏位していることであり，前尖のサイズ，弁輪径ともに正常であり解剖学的右室sinus部が膨隆することもない。臨床上，心不全症状が比較的急速に悪化する現象がみられるが，このメカニズムとしては内側乳頭筋が心室中隔に付着していることが心室の容量負荷により三尖弁弁尖のcoaptation不良による逆流を招き，それが更なる心室容量負荷となるという悪循環により説明される。

弁への到達法はconcordant heartと同様でよいが，その場合よりも弁の向きがより前額断に近くまたより心尖部よりに位置する関係で視野の獲得がより困難である。弁形成を試みる場合であっても上記の複雑な背景からその成功率が低いことを念頭において，弁置換を中心に考慮する。したがって，弁置換後の事故が少なくなる幼少時期以降の患者がその適応になる。乳児期に三尖弁閉鎖不全が重度となる症例をまれに経験するが，この場合はconventional repairの適応にならない。

2. anatomical repair (double-switch)

anatomical repairではdiscordantな房室関係とdiscordantな室大血管関係を共にconcordantな関係に修復する術式である。複雑な手術手技のために手術時間が遷延するにもかかわらず，非常に良好な早期成績が複数の施設から報告されている[9, 10]。この術式により，conventional repairで長期遠隔期に潜在的に生じうる解剖学的右室/三尖弁の機能不全を回避するのがねらいである。事実，少なくとも術後10年までの遠隔成績は当初の期待に沿う良好なものといえる[5]。適応に関しては施設間で大きなばらつきが存在し，可及的にanatomical repairを行う意見もある一方，心房内血流転換術にともなう洞不全や心房粗細動の発生や上大静脈/肺静脈の再狭窄，Rastelli型手術に伴う長期遠隔期のmortalityおよび各種morbidityの発生頻度の高さを懸念する意見もある。この術式の適応が狭い施設においても解剖学的右室機能不全に陥った症例，また乳児期に重度の三尖弁閉鎖不全が生じている症例，三尖弁straddling(たとえ軽度であっても)の認められる症例で行われる。

房室関係修復術としてSenning，Mustardが，室大血管関係修復術としてarterial switch，Rastelli型の術式の組み合わせが存在する。なお，double-switchという用語には現在混乱が見られarterial switchによる室大血管関係修復とSenning，またはMustardの組み合わせのみを指す専門家とanatomical repairの総称を指す専門家が混在している。

Senning，Mustardの心房内血流転換術をこの疾患に行う場合，心房中隔のmalalignmentが必ずみられること，またmesocardia/dextrocardiaがしばしば合併することにより，デザインの上で心房切開線やSenningのときの中隔flapにパッチ延長の必要性など，concordant heartの場合のものとかなり異なることが多い。

Rastelli術は肺動脈弁が機能的形態的に異常である場合に選択される。解剖学的右室からの心外導管の位置は胸骨の直下になることを避けて大動脈の左側(内臓心房位が逆位の場合は右側)を通して肺動脈に渡すことが望ましいが，肺動脈のサイズや位置により胸骨の直下を横切る形にならざ