the sternum veins bears some similarity to the opening of the cranial vault veins, and disconnecting the endotracheal tube just before sternotomy decreases airway pressure. Furthermore, 5 (25%) of our patients had a preexisting right-to-left shunt, again increasing the likelihood of clinically significant VAE. The fact that embolus incidence was higher with the saw compared with the scissors is not straightforward. It would seem that the saw would result in less compression of the bone marrow, thus being less traumatic. One may hypothesize that the vibration caused by the saw action induces microbubble formation such as in agitated saline. This hypothesis was tested by pressing the saw against the closed chest wall, thus testing the effects of the vibrations alone. No emboli were detected. Another explanation might be that the vibrations cause increased small amounts of air entrainment in the open vessels. This hypothesis has not been tested. In summary, our results suggest that VAE during sternotomy is a frequent occur-

rence and that the number of emboli is related to the method of sternotomy.

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First human transplantation of a bioengineered airway tissue

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Airway defects occurring at the anastomotic site after carinal pneumonectomy are associated with persistent contamination between airway and pleural spaces, mediastinal spaces, or both and difficulties in the re-expansion of and possible aspiration into the residual lung. Unfortunately, therapeutic interventions are limited, and the outcome is often fatal.¹ An ideal solution would be to generate an airway segment or surface to be implanted after achieving control of the infection and aspiration. Tissue-engineered airway is about the only technique of the many attempts at tracheal replacement that seems to offer any real promise.² It applies the principles of engineering and life sciences toward the development of biologic substitutes that restore, maintain, or improve tissue function and offers the potential to create replacement structures from biode-

gradable scaffolds and autologous cells.³ We here describe the first clinical application of a tissue engineered airway patch.

Clinical Summary

A 58-year-old man was admitted in April 2003 complaining of general weakness, coughing up of pus, temperature of greater than 39°C, shortness of breath, and intolerable halitosis. He had undergone a right completion carinal pneumonectomy and radical lymphadenectomy for a relapsing non-small cell lung cancer pathologically staged as T4 N0 M0 in March 2003. He had had an upper bilobectomy and adjuvant radiation therapy (60 Gy) for a non-small cell lung cancer of equal histotype staged as T3 N2 in 1999. On chest radiography, the air-fluid pleural level in the postpneumonectomy space vanished, and the contralateral left lower lobe showed infiltrative signs suggestive of aspiration pneumonia. Bronchoscopy showed a complete dehiscence of the ventrolateral aspect of the tracheobronchial anastomosis measuring 2 × 2 cm, communicating directly with the residual pleural space. Because *Pseudomonas aeruginosa* strains were found in the pleural space and blood, the diagnosis of pleural empyema and pyosepticemia was made, and the decision was taken to perform both ventral and dorsal open thoracostomies. The patient was further treated medically with the intent to sterilize the residual pleural space, prevent bacterial contamination of the residual left lung, and obtain a spontaneous closure of the anastomotic dehiscence.

The patient's general conditions improved slowly to an extent that his pleural space was uncontaminated, and his pyosepticemia resolved. However, on the basis of the previous bad clinical experiences,¹ written informed consent was obtained to take, after

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Figure 1. Process of engineering the bioartificial patch. Muscle cells and fibroblasts are isolated from a biopsy specimen obtained from the patient. These cells are seeded on a biologic matrix representing a collagen network generated from a decellularized porcine jejunal segment. During the incubation period, the cells start to remodel the xenogenic matrix and replace it with autologous connective tissue. Within 4 weeks, this autologous bioartificial implant can be clinically used. The computed tomographic scan of the chest 6 weeks after graft implantation shows the site (arrow) where the tissue-engineered patch was transplanted. The right pleural cavity is completely filled with the transposed omentum major and right subscapular muscle.

Figure 2. Histologic composition of the bioartificial patch. A, Acellular porcine collagen matrix. (Original magnification 200 $\times$ hematoxylin and eosin staining.) Notice the absence of cellular components and the red-stained collagen fibers. B, Reseeded patch before implantation. Antivimentin immunohistology depicting fibroblast and smooth muscle cell seeding. (Original magnification 200 $\times$.) C, Brush cytology from the patch surface showing respiratory epithelium (12th week). Arrows indicate epithelial cilia. D, Immunohistochemical staining for respiratory epithelium (12th week). (Original magnification 200 $\times$; Villin antibody.)

achievement of local anesthesia, tissue samples at the thoracotomy sites with the intent to generate a bioengineered airway tissue that could then be transplanted to close the anastomotic defect (Figure 1). The patient was then discharged. We isolated muscle cells and fibroblasts from the biopsy samples by means of trypsin–ethylenediamine tetraacetic acid digestion and expanded the cultured cells *in vitro*. After 3 weeks (third cell passage), 1.5 million cells were seeded on a 24×36 -mm matrix (5% muscle cells/95% fibroblasts). This carrier structure consisted of a collagen network that was generated from a decellularized porcine proximal jejunum segment (Figure 2, A and B). The resulting bioartificial construct was incubated for another 3 weeks in a bioreactor to control cell proliferation and to allow functional tissue formation by extracellular matrix turnover.⁴ Its maximal *in vitro* tolerance to pressure forces was then evaluated and found to be 300 mm Hg.

Five weeks later, the patient was readmitted for final defect closure. The results of clinical examination and blood tests were unremarkable, as were the results of complete tumor staging. Brush cytology of the pleural cavity showed normal respiratory bacterial flora and no evidence of any pathogenic bacterial colonization. Endoscopy showed a minimal reduction in the size of the airway defect and ruled out infections of the residual left lung. The patient underwent surgical intervention through the previous thoracotomy incision. The defect was immediately identified and mobilized, and the dehiscence was completely opened so that it could be measured as being 1.5×1.5 cm large. The pleural surface was debrided. The generated tissue-engineered segment was folded medially to double the graft's thickness and transplanted over the dehiscence by fixing it circumferentially to the neighboring mediastinal tissue with 4-0 polyglactin (Vicryl; Ethicon Inc, Sommerville, NJ) interrupted sutures anchored. Air tightness was confirmed intraoperatively, and the operation was completed with an omentum major and right subscapular myoplasty transposition and tailored thoracoplasty (second to fifth ribs). Both open thoracostomies were closed as well. The patient was extubated at the end of the operation and transferred to the surgical intensive care unit. Within the first hour after the operation, the patient had an acute pulmonary edema that was successfully treated with dehydration. The patient was transferred to the normal ward on the fifth postoperative day. The further postoperative course was uneventful, and the patient was discharged the third postoperative week. Control endoscopies with brush cytologies of the native trachea and transplanted patch were performed on the first postoperative week and after 3, 6, and 12 weeks on an outpatient basis. Cytologies were evaluated for reseeding cell type and viability. Pulmonary function tests and chest computed tomography were performed after 3, 6, 12, and 24 weeks.

Results

The patient can perform regular physical activity, enjoys hunting, and speaks with a sturdy voice. His quality of life has returned to normal. Clinical examination has been unremarkable, as has postpneumectomy lung function. Control endoscopy on the fifth postoperative day showed a tight airway covered by a normal mucosa and a graft that was laterally rigid but longitudinally flexible, therefore synchronizing the inspiratory and expiratory

movements. The graft's endoluminal aspect was surfaced with viable ciliated respiratory epithelium: its cellular density was 80% of that of the native trachea, and cell viability was almost 100%.

Outpatient endoscopies on the 3rd, 6th, and 12th postoperative weeks confirmed the above early postoperative findings and showed that the graft was airtight and surfaced with autologous ciliated respiratory epithelium (Figure 2, C and D), with no evidence of chronic inflammation, granulation tissue, infection, or erosion. Vascular ingrowth was detectable from the patch margins as soon as by the 6th week and completed by the 12th postoperative week. After 12 weeks, the entire patch was functionally and morphologically completely integrated into the adjacent airway. Chest computed tomography documented complete filling of the right pleural cavity.

Discussion

Tissue engineering implies formation of manmade functional biologic organs or tissue replacements by autologous cells introduced into a framework of biodegradable or biologic carrier structures, the so-called matrices.³ The advantages of the matrices are their biocompatibility, bioabsorbability, nonimmunogenicity, support of cell attachment and growth, and ability to induce angiogenesis.

The tissue-engineered airway patch used here was made from autologous muscle cells and fibroblasts seeded on a sufficiently large (24×36 mm) matrix consisting of a collagen network generated from a decellularized porcine proximal jejunum segment. This bioartificial graft was then successfully clinically transplanted. The time frame needed to prepare it was clinically satisfactory because it allowed the infection of the residual pleural space and contralateral aspiration pneumonitis to subside, the patients' general conditions to improve, and the defect to stabilize. Its technical transplantation was surgically straightforward, avoided the very risky mediastinal dissection,¹ and immediately guaranteed an airtight airway. Repeated bronchoscopies proved permanent closure of the defect and evidenced the graft's neovascularization *in vivo*. Most interestingly, however, was the demonstration that the tissue-engineered patch (1) was reseeded with functional ciliated respiratory epithelium, (2) had a cellular density equal to 80% of the native trachea, and (3) had almost entirely viable cells, and this was within the fifth postoperative day. This provides definitive evidence that a tissue-engineered airway patch with the dimensions used here can functionally survive and completely fills all requirements for an airway patch. A possible explanation for this phenomenon could be that the ingrowth of the respiratory epithelium from the normal tracheal ends alone was favored by the permanent viability of the bioengineered tissue. If this hypothesis holds true, there is no need for epithelial coverage and direct or indirect revascularization for tissue-engineered airway grafts of the dimensions used above.⁵

Conclusions

This anecdotal but encouraging experience unlocks the door for the clinical application of bioengineered airway tissue in other pediatric and adult pathologies in which therapeutic interventions are limited.

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Two-conduit repair for anomalous origin of the left coronary artery from the pulmonary artery in an adult

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Anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) presenting in adult life is rare. Although it is surgically treated in most cases, the preferred procedure offering the best short- and long-term outcomes is still unknown. We present the case of a patient who was successfully treated by a 2-conduit repair.

Clinical Summary

A 41-year-old previously healthy man presented with acute onset chest pain and left bundle branch block on his electrocardiogram. No increase of cardiac enzymes was detected. Echocardiogram showed a dilated and severely impaired left ventricle, but all valves were normal. Cardiac catheterization demonstrated a grossly dilated right coronary artery. The contrast material retrogradely filled a dilated left coronary system through the collateral vessels. The left coronary system in turn drained into the pulmonary artery (PA) (Fig 1). A contrast computed tomographic scan confirmed that the left coronary artery (LCA) was arising from the PA.

Surgical procedure. Anatomically it was not possible to translocate the LCA. Therefore, an intrapulmonary tunnel was constructed by first creating an aortopulmonary window; then, with a PA homograft patch as a baffle, the window was connected to the LCA ostium. In addition, the left internal thoracic artery (LITA)

was grafted to the left anterior descending artery (LAD). The patient made an uneventful recovery.

Coronary angiography was performed 6 months postoperatively and showed a patent intrapulmonary tunnel supplying the circumflex system and a patent LITA graft to the LAD. It also revealed a reduction in size of the coronary arteries (Fig 2). Left ventricular function improved (ejection fraction increased from 30% preoperatively to 40% postoperatively, and left ventricular end-diastolic diameter was mildly decreased from 65 to 60 mm on echocardiogram). In addition, the stress myocardial perfusion study demonstrated good perfusion, with no evidence of scarring. Clinically, the patient reported continued improvement in exercise tolerance.

Figure 1. Right coronary artery angiogram. Dilated right coronary artery (R) fills the LCA system (L) by collateral vessels (arrow).

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