

# History of Lung Transplantation

## *Akciğer Transplantasyonu Tarihçesi*

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### ABSTRACT

History of lung transplantation in the world dates back to the early 20th century, continues to the first clinical transplantation performed by James Hardy in the United States of America in 1963 and comes to the present with increased frequency. Over 40.000 heart-lung and lung transplantations were carried out in the world up to 2011. The number of transplant centers and patients is flourishing in accordance with the increasing demand and success rate in that arena. Lung transplantations that started in Turkey at Süreyyapaşa Teaching Hospital for Pulmonary Diseases and Thoracic Surgery in 2009 are being performed at two centers actively to date. This review covers a general outlook on lung transplantations both in the world and in Turkey with details of the first successful lung transplantation in our country.

**Keywords:** Lung transplantation, heart-lung transplantation, history

### ÖZET

Dünyada akciğer transplantasyonu tarihçesi, deneysel çalışmaların yapılmaya başlandığı 20. yüzyılın ilk yıllarından itibaren James Hardy' nin Amerika Birleşik Devletleri'nde 1963'te yaptığı ilk klinik transplantasyona uzanır ve hızlanarak günümüze gelir. 2011 yılına kadar dünyada 40,000'in üzerinde kalp-akciğer ve akciğer transplantasyonu yapılmıştır. Transplantasyon alanındaki artan ihtiyaca ve başarılarla paralel olarak transplant merkezleri ve hasta sayıları da giderek artmaktadır. Türkiye'de 2009 yılında Süreyyapaşa Göğüs Hastalıkları ve Cerrahisi Eğitim ve Araştırma Hastanesi' nde başlayan akciğer transplantasyonları günümüzde iki merkezde aktif olarak yapılmaktadır. Bu derlemede, ülkemizdeki ilk başarılı akciğer transplantasyonu detaylandırılarak dünyada ve ülkemizdeki akciğer transplantasyonu tarihçesi gözden geçirilmektedir.

**Anahtar Kelimeler:** Transplantasyon akciğer, transplantasyon akciğer-kalp

## HISTORY OF LUNG TRANSPLANTATION

*From dreams to reality*

*"It is only by virtue of experience that we live our lives, not by the information we are given."*

*Jeffrey Zeig*

Lung transplantation is now an accepted treatment modality for end-stage respiratory failure and an effective palliative method for carefully selected patients. According to the International Society for Heart and Lung Transplantation (ISHLT) 2012 registry, over 35.000 lung transplantations were carried out in centers worldwide starting from the eighties until 2011 (1).

Several attempts in lung transplantation had been made in Turkey, starting from 1998, but the real success, the patient's possibility of being discharged from hospital and surviving for years, was not apparent until 2009.

Being among the few privileged doctors to witness the first successful lung transplant operation in Turkey, it is my distinct honor and pleasure to be given the opportunity to write a review in 'Solunum' about the history of lung transplantation in the world and in our country. After giving a brief history of lung transplantation in the world, I will go into detail concerning the attempts of lung transplantation, with greater emphasis on the very first successful lung transplantation of Turkey.

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### Historical overview of heart-lung and lung transplantation in the world

In transplant history, we owe much to Alexis Carrel who worked on cell and tissue cultures in the early years of 20th century whose efforts enabled the very first experimental heart transplant in 1905 by himself and Charles Guthrie of Chicago University (2).

The journey of lung transplantation began much later when Vladimir P. Demikhov (1916-1998) performed the world's first experimental intrathoracic transplantation. Originally a Russian biologist, physiologist and pathologist, Demikhov experimented on dogs and performed transplantations of heart, lung and heart and lungs together in early 1946. His longest survivor lived for only 9.5 hours. His success heralded the era of modern heart and lung transplantation which was at that time neglected and underestimated. Although Demikhov was one of the greatest experimental surgeons of the previous century, he was isolated in the international surgical community until very late in his career partly because he published his articles in Russian and his experiments were mostly deemed eccentric and unethical. His transplantation of a dog's head to another dog drew much media interest and spread around the world more rapidly than any other medical report of his experiments (2-4). Until 1962 his experiments had not been published in English. His experiments were mainly on dogs and he proved that lungs could still be functional without bronchial circulation and innervation (4).

Clinical lung transplantation was carried out by James D Hardy (1918-2003) at the University of Mississippi in the USA. The recipient, John Russel, aged 60, was a prisoner sentenced to death who suffered from central, left-sided carcinoma of the lung. Because of his poor lung function, he was inoperable and to make things worse, he had chronic glomerulonephritis at the same time. Lung transplantation was carried out on June 11<sup>th</sup>, 1963, after which the patient had immediate satisfactory lung function. The postoperative course was complicated by renal failure and death occurred on the 18<sup>th</sup> postoperative day. This very first case of lung transplantation was greeted with great interest both in the media and medical world (2,5).

Between 1963 and 1969, out of 23 reported lung transplantations, there was one single success from Belgium on 14 November 1968. The surgeon was Fritz Derom and the patient was a young man with silicosis who survived for 10 months. Then there was again a long way and much experimental work to retrials. Complications, mainly infection and rejection, or technical difficulties slowed down the progress. Two thirds of approximately forty attempts up to 1980 resulted in bronchial complications, which forced surgeons to go back to the laboratory. Experimental work by JD Cooper and H Grillo proved that excess steroids had to be avoided. End to end anastomosis and omentopexy for neovascularization led to better results (5). In the meantime, in the USA, Denton A. Cooley from Houston attempted to carry out the first heart-lung transplantation on 15 September 1968, but the real success in this field came from Bruce Reitz and Norman Shumway of Stanford University in 1981 after the approval of cyclosporine in transplantations. The recipient was a 45-year-old lady with primary pulmonary hy-

per-tension. The donor was a 15-year old boy who was brain dead due to a severe head injury. The patient was extubated at 36 hours and was well enough to leave the hospital toward the end of the third postoperative month and attained a normal functional level at 10th month. This patient lived for more than 5 years (6).

Finally the first successful unilateral lung transplant was achieved by the Toronto Lung Transplant Group (Joel Cooper, Alex Patterson and colleagues) on 7 November 1983 followed by bilateral transplantation three years later by the same group (2,5,7).

### Attempts of heart-lung and lung transplantation in Turkey

The first pediatric heart-lung transplant patient was operated on by Oztekin Oto at Dokuz Eylul University Hospital in 1998. Six heart-lung transplants have been carried out in Turkey up to now, but none of the patients survived for long periods. Rather than scientific literature, my actual knowledge depends on personal communication with cardiovascular transplant centers within the country. Only the first patient is reported to have lived for nine months (8,9).

Göksel Kalaycı from Istanbul University attempted an adult bilateral lung transplantation on 11 October 2004. The patient was a 44 year-old male idiopathic pulmonary fibrosis (IPF) case. He had very high pulmonary arterial pressures and his kidney function was suboptimal. The donor was a very young female patient with a clear chest X-ray and favorable blood gases. The bilateral sequential single lung transplantation was carried out under cardiopulmonary by-pass that lasted 3 hours 50 minutes.

The patient had a bleeding disorder thereafter and died from disseminated intravascular coagulopathy and multiorgan failure on the 11<sup>th</sup> postoperative day. The postmortem biopsies from the lung showed acute alveolar damage. This very first case was followed by another IPF case the same year and another case in 2007, but none of the patients survived the early postoperative period. Data concerning those patients has been obtained by personal communication with Alper Toker who was in the transplant team in those days.

In 2008 an Eisenmenger patient received a heart-lung transplant at Ege University and this patient is said to have lived for a few months.

In 2012 another patient with heart failure and high pulmonary vascular resistance received a heart-lung transplant at Istanbul Kartal Kosuyolu Yuksek Ihtisas Teaching Hospital for Cardiovascular Diseases and Surgery, mainly recognized as a cardiac transplant hospital and a leading center in Turkey with over 100 cardiac transplants since 1989. The operation was performed by cardiovascular and thoracic teams guided by Mehmet Balkanay and Cemal Asım Kutlu. Unfortunately the patient did not survive the early posttransplant phase due to disseminated intravascular coagulopathy (DIC) and ensuing multiorgan failure.

### The first successful lung transplantation in Turkey

The first long-time lung transplant survivor of Turkey was a 34 year-old silicosis patient who underwent lung transplantation

at Sureyyapasa Teaching Hospital for Pulmonary Diseases and Thoracic Surgery on 7 March 2009. The procedure was carried out by a surgical team headed by Cemal Asim Kutlu at a state teaching hospital, and this operation has given hope and opportunity both to patients and doctors in the country (10). Although criticized and questioned for quite a long time, this very first case started a surge of interest in lung transplantation in the country. Soon after, Mustafa Özbaran performed the first bilateral pediatric lung transplantation at Ege University on 8 April 2009 (11). The patient, a 15-year-old teenager, primarily diagnosed with bronchiolitis obliterans who was in the latest stage of his disease, lived for nearly 3 years after the operation. He was well until he developed chronic rejection late in the second year and died due to bleeding complications after retransplantation was attempted at Kartal Kosuyolu Yuksek Ihtisas Teaching Hospital for Cardiovascular Diseases and Surgery.

Several attempts were made in Turkey starting from 1998, but the real success, with the possibility of the patient being discharged from hospital and surviving for years, was not apparent until 2009. As the pulmonologist of the team, I witnessed the first successful lung transplant operation and I would like to give our readers a glimpse of behind-the-scenes in this operation. What happened at Sureyyapasa in those days is mainly the result of the synergy of a group of enthusiastic doctors committed to establishing a lung transplant program at their hospital. Up to that time, although Turkey had a few transplant centers, prominent institutions, mainly university hospitals, were reluctant to enter this arena because of concerns about outcomes and difficulties concerning boundaries of specialties to deal with lung transplantation. With this historical background in 2007, Semih Halezeroglu, the medical director of the hospital in those days and Cemal Asim Kutlu, the director of the prospect transplant program were determined to change the regulations concerning lung transplantation in Turkey. The regulation, at the time that it was prepared, said that lung transplantation could only be carried out by cardiovascular surgeons who were at the same time thoracic surgeons, but in Turkey cardiovascular surgery and thoracic surgery had been two distinct specialties since a long time. That meant that thoracic surgeons were to deal with lung transplantations. Since it took quite a long time for negotiations at the level of the Ministry of Health to make the desired change in the regulation, the team at Sureyyapasa namely Sureyyapasa Lung Transplantation Study Group made the start for a visionary change. Medical and technical needs were met, members of the team were sent abroad and to cardiovascular centers in Istanbul to have proper training in transplantation. Weekly seminars and literature reviews were organized with invited speakers from transplant centers. Logistic problems and legislative issues were addressed. Finally the certification of Sureyyapasa as a transplant hospital was completed in December 2008. In the meantime, patients were accepted and evaluated preoperatively to form a waiting list. In a few months' time we had nearly 30 cases on the waiting list because the demand from the doctors and patients increased as soon as news spread in the medical community.

There was both excitement and anxiety when the first lung donation was announced to Sureyyapasa late in the afternoon

on a Spring day (6 March 2009). The donor was a 13-year-old female patient who had brain damage due to a motorcycle accident and was announced 'brain dead' after being intubated for 72 hours. Her chest X-ray and bronchoscopy findings were normal.  $PaO_2/FiO_2$  was greater than 500 which was quite good. The only difficulty would be to find a recipient with a small-sized chest cavity. When we looked at our waiting list, we found that the matching recipient was a 34 year-old dental technician who suffered from silicosis related to his occupation. He had been suffering from respiratory distress for the last 11 years, was on oxygen and his condition was deteriorating rapidly. The patient and his relatives were called to the hospital so as to make final preparations while Cemal Asim Kutlu, Erdal Tasci, Oral Akin and our coordinator Belma Erdoğan flew to Konya to get the donated lungs. During the time we prepared the patient medically and psychologically on the ward, another team in the operating theatre was getting ready for pneumonectomy. As soon as they were informed that the organs were in perfect shape and function, they started the operation on the recipient just before midnight.

What motivated us for success was our patient who was so young and so eager to survive the operation. We knew that we could fail, but the desire to succeed dominated the anxiety shared by all.

The operation went "smoothly", as surgeons say. The implantation of the new lung was complete at dawn and the patient was transferred to the intensive care unit with his new left lung (Figures 1, 2). In spite of unpredictable complications like hypothermia and metabolic acidosis, predictable complications and drug reactions occurred as well, but we were hopeful when the patient was extubated at 15 hours. There was great joy and excitement at the hospital and the news spread quite fast in medical surroundings.

The very first patient of lung transplantation lived for 3.5 years. He endured rejection episodes and infections but developed bronchiolitis obliterans syndrome earlier than expected mainly owing to his medical noncompliance and gastroesoph-



**Figure 1.** Donor's left lung in the surgeon's hands (right) and the explanted silicotic lung of the recipient (right corner) (The first long-time lung transplant survivor of Turkey)



**Figure 2.** The posttransplant chest X-ray of the very first patient (left lung transplanted)

ageal reflux and died of a massive hemoptysis while awaiting retransplantation (**Figure 3**).

By the time I went to the United Kingdom for my second training in lung transplant medicine, 7 transplants had been performed, of whom only 2 survived. The patients were either lost due to surgical problems or primary graft dysfunction and ensuing infections. We announced our data at national meetings which was met by excitement and criticism at the same time. We were questioned as to whether we were right in our patient selection, donor selection, harvesting and organ procurement and matching. We had limited resources. Administrative problems with drug maintenance, drug level monitoring, and bronchoscopy practice complicated the course of establishing a well-organized program. We were accused of draining our hospital's resources into a costly procedure, but having less favorable prognosis when compared to outcomes of world centers. On the other hand, there was a huge demand both from our patients and their families which was a source of motivation but a great responsibility and burden at the same time. We were under the scrutiny of the medical community, which put much pressure on team members.

The operations and the postoperative period were also questionable. These were all part of a lung transplant program and our circumstances were not perfect, starting with the choice of recipients. Some of our cases were functionally too desperate to survive a critical operation like transplantation with a low capacity of rehabilitation. Some of them were disabled by their respiratory insufficiency, were on noninvasive ventilators, bedridden and psychologically and socially in poor condition. These were relative or sometimes arguably absolute contraindications to transplantation, but we also had patients that surprised us with their prognosis having a strong drive to survive in spite of all complications. After time has elapsed, we can see that the results were really frustrating at the beginning and we discussed our cases with international authorities to improve our program. We also had to withstand administrative obstacles like medical expenses, drug maintenance, drug level monitoring, bronchoscopy performances, all of which are essential



**Figure 3.** The first case in his third posttransplant year. Chest X-ray shows total opacification on the left (chronic rejection)

parts of a transplant program. Several prominent centers found it challenging to enter the transplant arena because of concerns about outcomes and drawbacks of current circumstances in the country. One year later, determined to carry on, Cemal Asim Kutlu and his team moved to another hospital (Kartal Kosuyolu Yuksek Ihtisas) to search for better surgical and intensive care possibilities. Since then, they have transplanted a total of 30 cases. Now at the same center, we are faced with patients who are more severely ill with comorbidities, heart-lung transplant candidates, even patients with multiorgan failure, a higher number of borderline donors and overall reduced resources in healthcare due to changes in health management.

In the meantime the number of certified centers in Turkey increased to 7 with the support of the Ministry of Health. The characteristics and number of transplant centers needed for our country is a matter of debate and deserves another review. To me, less is more and it is not only the number of transplants done, but the quality of patient management and follow-up that will make a transplant center accomplish its goal in the international transplant community.

In my opinion, there are numerous factors that should be taken into account while establishing a lung transplant program. Forming a transplant team with dedicated and competent members is of utmost importance. Transplantation goes far beyond surgery. The transplant surgeon is the founder, pioneer and usually the chief of a lung transplantation program. The transplantation process, although guided by a surgeon, is more than surgery itself and requires many elements and participants besides surgeons. A lung transplant team should consist of a pulmonologist, infectious diseases specialist, anesthesiologist, intensive care specialist, cardiovascular surgeon, psychiatrist or psychologist, pathologist, immunologist, pediatrician, dietitian, physiotherapist and a transplant coordinator. Although historically correct and well-functioning, 'a surgeon as the leader and his followers' is actually an old-fashioned and politically incorrect method of lung transplant organization. Delegation of responsibilities and duties and checking the output of the team could be a better solution to team work control. Pulmonary physicians in

that regard, work hand-in-hand with surgeons and should not be dominated by surgeons, because today's transplant medicine has encountered vast developments in immunology, intensive care and infection control over the past decades and transplantation is no longer a mere field of surgical interest and competency.

As outlined above, the driving force of a transplant team is the human force. As far as complications and risk of mortality are concerned, lung transplantation prevails over other solid organ transplants and necessitates a serious team working, sharing information and experience, personal dedication and sacrifice. It is essential to create a nucleus of interest in all team members so that the team functions at its best.

After establishing a well-organized transplant program, Adnan Sayar from Yedikule Teaching Hospital for Pulmonary Diseases and Thoracic Surgery, succeeded in transplanting a single lung to a 29-year-old male alpha 1 antitrypsin deficient patient on 14 March 2012. The donor was a 44-year old male patient who was brain dead due to an intracranial aneurysmatic rupture. The duration of cold ischemia was slightly over 5 hours. The operation went well and patient was extubated in a few days' time without major complications in the early postoperative phase. Yedikule Transplant Group has transplanted 12 patients in 11 months and only three patients died in the early posttransplant period. Two other patients died in their 4<sup>th</sup> and 7<sup>th</sup> months, due to unknown cause and septicemia respectively. The Yedikule Group has made steady progress in a short time. As of February 2013, the last three operations were carried out with ECMO support intra- and postoperatively as needed. One transplant operation was carried out in another city with donor organs coming from another city, which might in fact hamper the coordination process, but was managed well.

Because organ donation is not at its best rate and the number of available organs is not as high as it should be, there is a scarcity of donor lungs in Turkey as in other countries in the world. That is why non-heart beating donors or marginal donors can also be used for transplantation as well as living-related lung transplantations. The Yedikule Transplant Group has once used lungs from a non-heart beating donor without major complications in the early postoperative phase. Living-related lung transplantation is an accepted treatment modality especially in Japan where cadaveric donations are scarce due to religious and cultural reasons. The Los Angeles Transplant Group has succeeded in achieving a reasonable number of successful living-related lung transplantations in the USA (12). Only one lobe can be taken from one living donor because of the operative risk. Two donors are needed for a bilateral transplantation. Ideal candidates for the procedure can be children or young adults who might have a high mortality if kept on the waiting list for a brain-dead donor.

I have learned from our limited experience so far that, while starting a lung transplant program, it is crucial to select good recipients, good donors, start with single lung transplants until competency is gained and work together as a team. In the current transplant era, transplantation is a complex process extending from a potential candidate to patient selection, donor

selection, the operation itself, the early postoperative period, immunosuppressive therapy, infection control, rehabilitation and life as an outpatient. All these steps require a sophisticated network of care and communication, not only to carry out the daily work, but to promote productive inpatient care, clinical and sometimes basic research (13).

Regardless of some questioning and inappreciative attitudes towards today's lung transplantation adventure in Turkey, ongoing attempts and work have touched at least some patients and their families and encouraged doctors and patients to continue with what seemed impossible only 4 years ago. The passage of time will allow us all to value the true impact of efforts from a different perspective and have the appropriate appreciation for the contribution of all members of the transplant team. In spite of difficult circumstances, I believe these initial attempts have served and will serve the development of heart-lung and lung transplantation in our country.

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**Hakem değerlendirmesi:** Dış bağımsız.

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