CASE REPORT

Heart-lung transplant: *Pedes in terra ad sidera visus.* Case report and review of the literature

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Heart-lung block transplant is currently a modality for some patients with advanced and refractory cardiopulmonary disease.The survival rate is 70% at one year. Causes for early postoperative mortality, are graft failure and hemorrhage. Late complications are complex, from cardiac allograft vasculopathy to bronchiolitis obliterans, and malignancy, with skin cancer being the most frequent. Currently 80-90% of the patients receive some type of pharmacologic therapy for induction, the typical regimen for immunosuppression maintenance is tacrolimus and mycophenolate. We present a case of severe pulmonary hypertension and ASD , treated successfully with a heart-lung block transplant.

Key words: **Pulmonary hypertension; Procurement; Transplant, heart-lung; Transplantation.**

El trasplante de corazón-pulmon en bloque es una modalidad aceptada para algunos pacientes con enfermedad cardiopulmonar avanzada. Actualmente la sobrevida es 70% a 1 año. Las causas de mortalidad postoperatoria temprana suelen se falla del injerto y hemorragia. Las complicaciones tardías son complejas, desde vasculopatía del aloinjerto cardiaco y bronquiolitis obliterante, hasta malignidad, siendo el cáncer de piel el mas frecuente. Actualmente 80-90% de los pacientes reciben terapia farmacológica de inducción. La terapia de mantenimiento se basa principalmente en tacrolimus y micofenolato. Presentamos un caso de hipertensión pulmonar severa y CIA, sometido exitosamente a trasplante en bloque de corazón-pulmon.

Palabras claves: **Hipertensión pulmonar; Procuración; Trasplante, corazón-pulmón; Trasplante.**

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It has been 49 years since Dr. Cooley performed the first heart-lung block transplant in a two-year old patient, who only survived for 14 hours. Since then through time and improvements in the surgical technique, anesthesia, immunosuppression, the long-term survival rate has successfully increased. In 1988, Reitz et al. [1] published the first case series with successful results.

Currently, most of the heart-lung transplants are performed on patients with severe pulmonary hypertension associated to congenital heart disease **(Fig. 1)** [2]. The following are specific clinical indications: i) Eisenmenger's syndrome associated to an intracardiac defect that has not been corrected, or failed correction; ii) congenital heart disease not amenable to correction associated to atresia and/or severe pulmonary artery hypoplasia and heart failure; iii) coexisting severe cardiopulmonary disease associated to advanced heart and/or pulmonary disease; and iv) severe heart failure (Class D) with biventricular disfunction associated to secondary pulmonary hypertension unresponsive to vasodilators.

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It is important to mention that patients with pulmonary arterial hypertension that is refractory to medical treatment, with the exception of those with biventricular failure, are treated better with bilateral lung transplants. Of note, there is a small tendency to perform a heart-lung block transplant in select patients with interstitial lung disease, and it is rare in those with cystic fibrosis.

Taking into account that Eisenmenger's syndrome natural disease progression has not been completely explained, the precise moment to initiate a block heart-lung transplant is not so clear. However, it is accepted to consider the following factors: i) worsening functional status; ii) cyanosis and progressive oxygen desaturation, particularly when the maximal oxygen saturation is 60% during exercise and frequent phlebotomies are needed; iii) progressive right ventricular failure with deterioration in the following ancillary clinical findings: TAPSE and diameter index by echocardiography, stroke index and PaPi (pulsatitlty arterial pulmonary index).

International statistics/transplant centers

The heart-lung annual transplant number remains low, with only fifty-two procedures performed in 2016 **(Fig. 2)** **(Fig. 3)** [1,2]. Seventy percent of the heart-lung block transplants in the last three decades have been performed due to

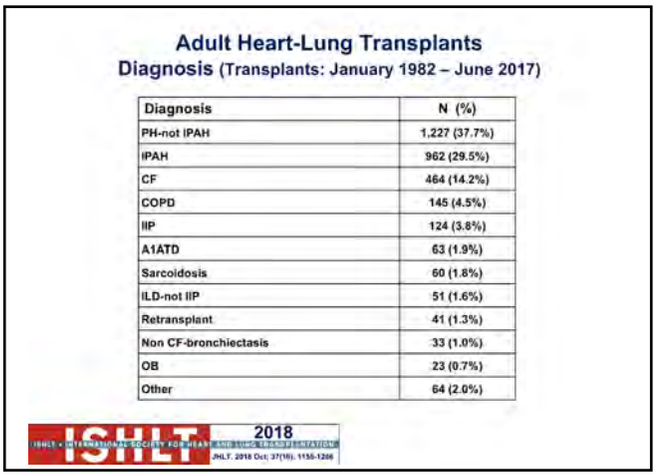

Figure 1. Diagnosis in cases for adult heart-lung transplants.
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pulmonary hypertension, primary or secondary. As mentioned previously, the tendency to perform these transplants in patients with interstitial lung disease is small [3].

Despite most of the recipients being younger than 50 years of age, there has been an increase in patients older than 50 in recent registries. Between January 2004 and June 2017, 32% of the patients in the United States were older than 50 at the time of transplant [4].

CASE REPORT

We present herein the case of a 16-year-old male with a diagnosis of severe idiopathic pulmonary hypertension in the year 2015, associated to ostium secundum atrial septal defect. He was initially diagnosed with asthma during childhood and had no other significant medical history. Throughout the years he developed progressive dyspnea, central and peripheral cyanosis. He had a normal oxygen saturation at rest dropping to 80% during exercise and requiring 25 L/min of oxygen to maintain a normal saturation.

Physical examination was significant for cyanosis and a heart murmur which ultimately led to additional testing. Transthoracic echocardiography showed LVEF 55%, mild mitral valve regurgitation, moderate tricuspid valve regurgitation, moderate to severe right ventricular failure. Ostium secundum atrial septal defect with right to left shunting. Ventilation perfusion scan: Left lung VQ 39%, right lung VQ 61%. Creatinine clearance: 61 ml/min. Blood group: AB. HLA: Class I 3%, Class II 0%. Chest CT: dilated main pulmonary artery, lung parenchyma with changes suggestive of plexiform arteriopathy consistent with pulmonary hypertension **(Fig. 4)** **(Fig. 5).** Right heart hemodynamic study: right atrial pressure 7 mmHg, Pulmonary artery pressure 95/42/68 mmHg, pul-

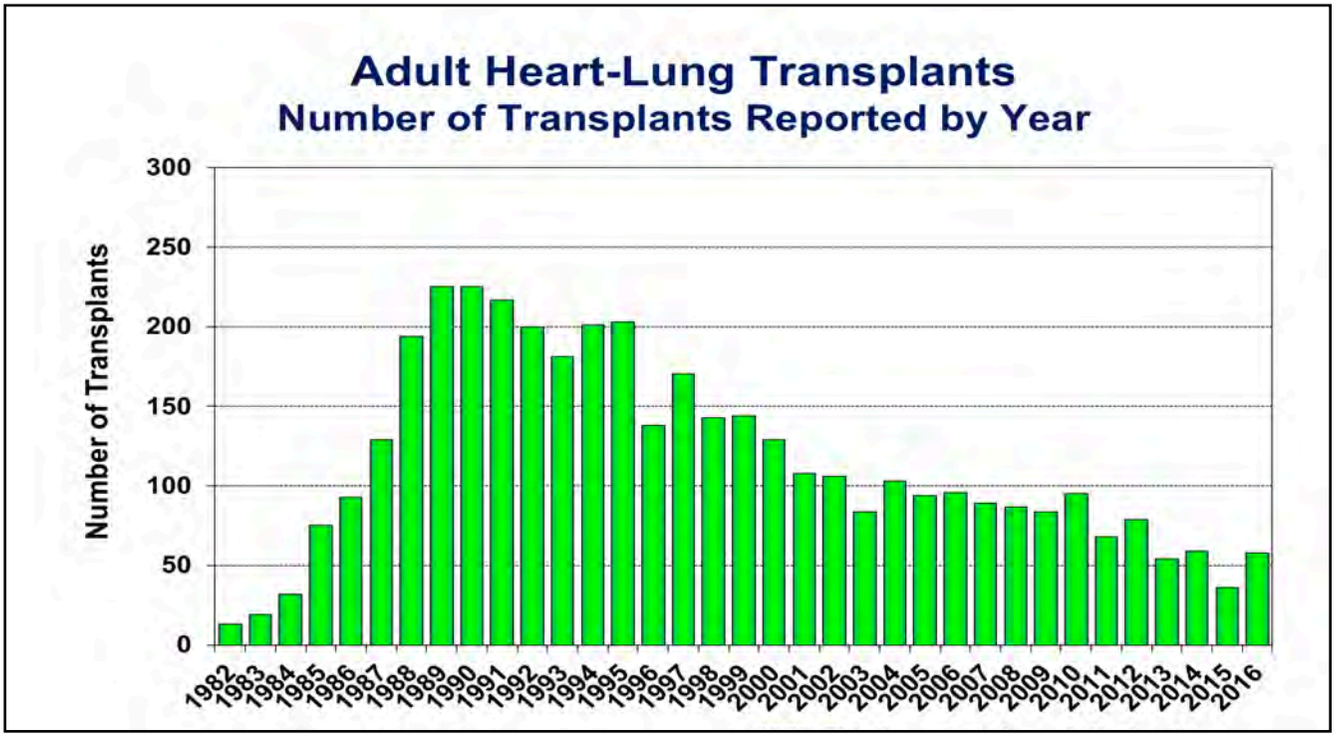

Figure 2. Number of adult heart-lung transplants reported to the International Society of Heart and Lung Transplantation Registry by year (transplants: 1982-2016).
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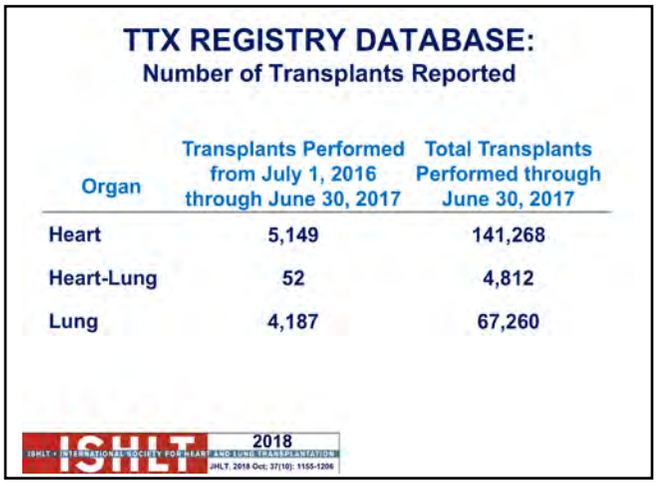

Figure 3. Number of transplants reported from 2016 to 2017.
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monary wedge pressure 8 mmHg, pulmonary vascular resistance index 24.7, cardiac index 2.3.

He was initiated in July 2015 on ambrisentan and tadalafil. By October 2017, treprostinil was added as a third agent. During this time, he is in an oral anticoagulation regimen based on Warfarin with a target INR between 1.5 and 2.5. Despite therapy the pulmonary arterial pressures remain elevated and his functional class progressively deteriorates. As a result, he was considered as a candidate for heart-lung block transplant. After approximately 6 months in the waiting list, a blood compatible donor with an acceptable weight, height, lung dimensions and total lung capacity index was found and accepted as a donor. Serology for the receptor/donor was composed of citomegalovirus receptor negative/donor positive, Epstein Barr virus receptor negative/donor positive, Toxoplasma receptor and donor negative.

Procurement technique

After the median sternotomy, thymus separation and pericardial incision, we proceeded to inspect and value the integrity of the heart and lungs. Once the organs were considered appropriate for transplant, the superior vena cava was dissected up to the innominate vein where the junction is used as a point for ligation. Subsequently the azygous vein is double ligated. The aorta is separated from the pulmonary artery up to the level of the ligamentum arteriosum. It is important to secure a complete dissection plane throughout the circumference of the ascending aorta, aiming to for a total and effective occlusion with the clamp during cardioplegia [5].

In coordination with the abdominal organ transplant team and the different receptor teams, heparin was administered, the cardioplegia cannula was placed into the ascending aorta close to the sinotubular junction. The pulmoplegia cannula was placed in the pulmonary artery bifurcation (an angulated cannula is recommended, in which is directed to the pulmonic valve) Left-sided decompression was performed through the left atrial appendage, clamping the appendage with a Satinsky clamp and cutting above the clamp is recommended. Prostaglandin E1 is administered directly to the pulmonary artery. The superior vena cava is ligated, the inferior vena cava is partially trans-sectioned. The heart beats empty briefly and a clamp is placed to completely occlude the ascending aorta. Immediately after the Satinsky clamp holding, the left atrial appendage is released while the lung and heart perfusion is initiated. It is recommended not to release the Satinsky clamp before applying the aortic clamp, since this could fill the surgical field with blood and impair adequate aortic clamp placement. Ice is placed over the heart surface and all over both pleural spaces. Adequate aortic root pressure is verified manually in addition to a complete cardiac decompression and

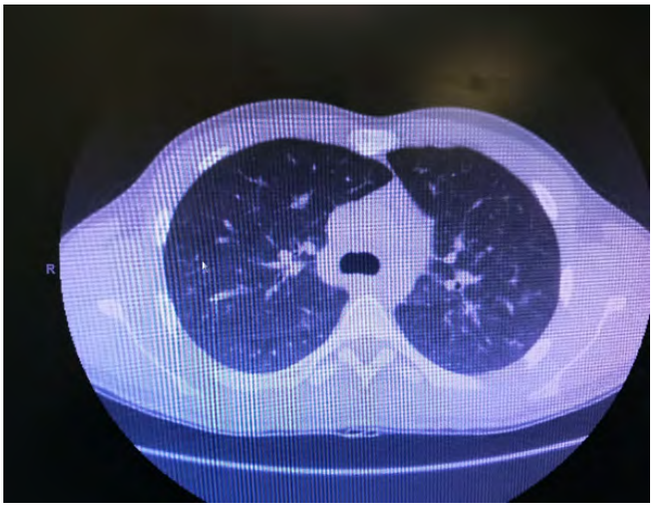

Figure 4. Chest CT showing parenchimal changes of pulmonary hypertension

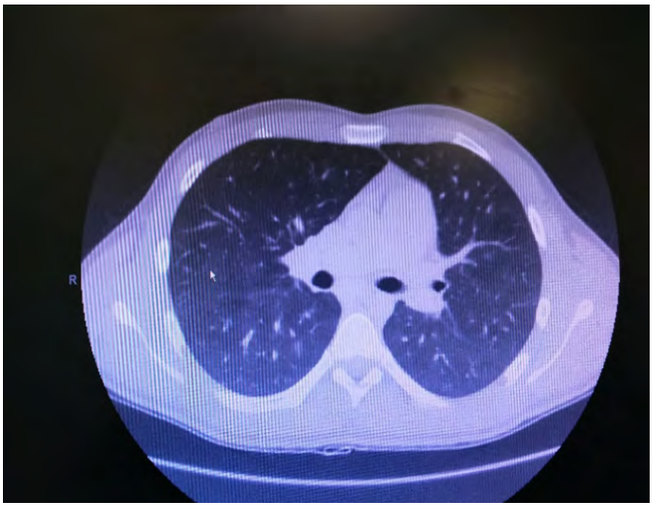

Figure 5. Chest CT showing an enlargement of the pulmonar artery.

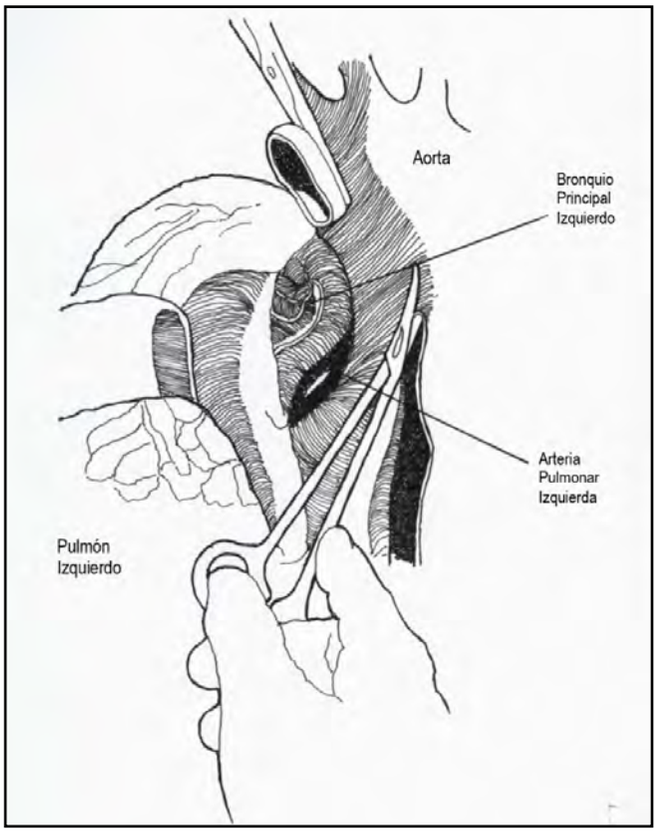

Figure 6. Dissection of the posterior mediastinum, begining with the left lung.

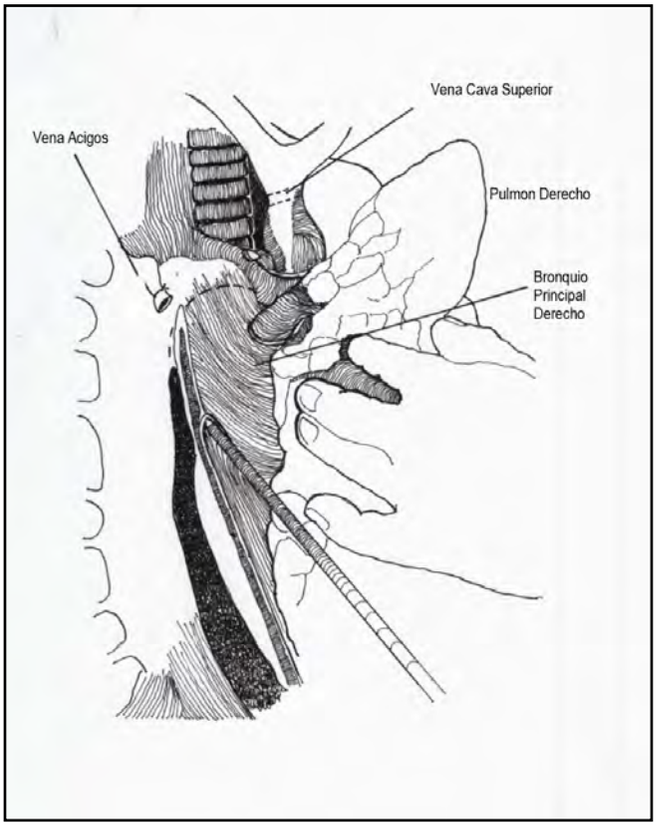

Figure 7. Dissection of the heart-lung block in the posterior mediastinum, right lung.

free drainage through the left atrial appendage. Throughout this the lungs continue to be gently ventilated.

Once the organ perfusion is terminated the aortic clamp and both perfusion cannulas are removed. The superior vena cava, azygous vein, aortic arch and inferior vena cava are trans-sectioned. Subsequently dissection of the anterior pericardium and both phrenic nerves is pursued and both pulmonary ligaments are completely cut. After the plane between the posterior pericardium and esophagus is dissected, the innominate vein is sectioned, the trachea is identified and circumferentially dissected. Then the endotracheal tube is removed to the level of the vocal cords and the lungs are inflated to reach an adequate expansion volume (generally with a Valsalva maneuver of 10 mmHg). Simultaneously the trachea is double stapled with a TA30 device and divided.

Attention is now directed to the heart-lung block extraction in the plane previously found between the posterior pericardium and the esophagus. It is initiated by left lung retraction to the right. With blunt and cutting dissection always adjacent to the esophagus **(Fig. 6)**, the mediastinal tissue is entirely dissected until the previously sectioned trachea is found out. The procedure is repeated but now retracting the left lung towards the right. Here, it is essential to conserve the plane adjacent to the esophagus to avoid damaging the airway or pulmonary veins **(Fig. 7)**. The posterior dissection is completed that way and the heart–lung block is now extracted **(Fig. 8)**.

Explant technique

In the inmediate preoperative period the recipient was administered azatriopine 4 mg/kg and methylprednisolone 40 mg. Basiliximab 20 mg IV was administered during induction and surgery is begun with a median sternotomy. All adhesions in the pleural spaces are dissected before heparinization, making sure the complete lung separation. The recipient is subsequently heparinized, the aorta and both venae cavae are cannulated, the superior one close to the union between the innominate vein, while the inferior one near the diaphragm. This secures optimal segments for the subsequent anastomosis **(Fig. 9).** Alternatively, the inferior vena cava can be cannulated through a femoral route. Once cardiopulmonary bypass is initiated, the clamp for total ascending aortic occlusion is placed. Cardiectomy is performed after bicaval, great vessel and pulmonary vein transection **(Fig. 10).**

Afterwards, bilateral pneumonectomy is performed by isolating the pulmonary hilum and the block is trans-sectioned (arteries, veins and bronchi). Using a TA60 stapler device, placing double staples and sectioned hilum both lungs are extracted. All the residual tissue from the right pulmonary artery is resected. The left pulmonary artery is preserved to prevent nerve damage. Now, the trachea is identified, and

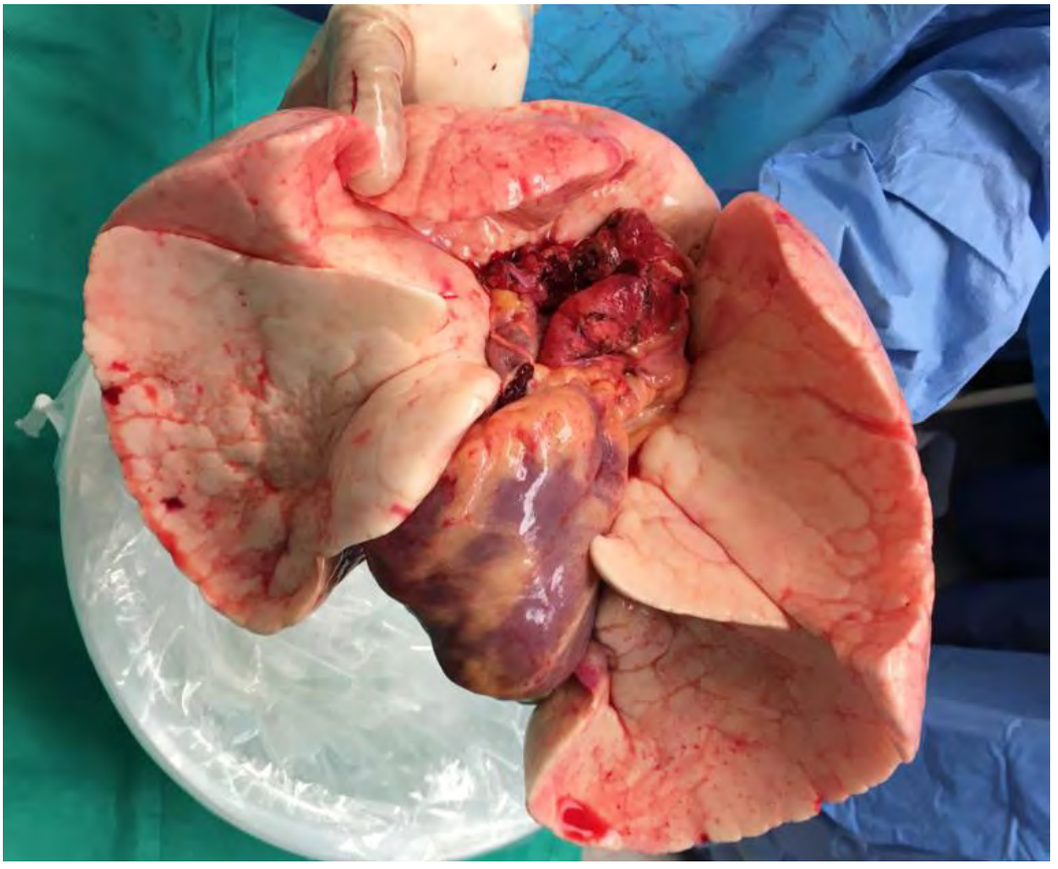

Figure 8. Heart-lung block.

double stapling is performed using a TA30 with subsequent transection above the carina **(Fig. 11)**.

In order to prepare for the heart-lung block placement, a bilateral incision in the pericardium is performed, posterior to the phrenic nerve and immediately anterior to the pulmonary hilum (previously trans-sectioned) up to the diaphragm **(Fig. 12).** This incision has to be large enough to allow for adequate lung placement in thoracic cavity [5,6].

It is of paramount importance to secure hemostasis of all the tissue in the posterior mediastinum, including absolute control of the residual bronchial arteries. Once the heart-lung block is inserted, visualization of this anatomic region becomes impossible.

Implant Technique

Once the explant is complete, the heart-lung block implant is performed. The first step includes releasing the staples from the trachea, which allows collapsibility of the lung tissue, so that both can be placed in their respective pleural cavities through the pericardial incisions previously described **(Fig. 13)** [5,6].

The tracheal anastomosis is the first to be performed with a continuous PDS 4/0 suture. After the implant placement is completed by performing an anastomosis of the aorta and inferior vena cava with prolene 4/0 running suture **(Fig. 14)** [6]. One of the most feared complications is tracheal anastomosis dehiscence. With this regard, multiple reports have been described using omentum, pericardial tissue and intercostal muscle tissue with a wide range of success rates [8-12].

The aortic clamp is released with adequate de-airing through the root, verified by transesophageal echocardiography as well. Superior vena cava anastomosis is performed with a 5/0 prolene continuous suture. Tourniquets from both venae cavae are released. Patient is ventilated with a tidal volume of 500 ml, FiO2 60% and the cardiopulmonary bypass is removed without difficulty. Flexible bronchoscopy demonstrates the integrity of the anastomosis without bleeding and reperfusion injury. In this case herein, the total ischemic time was four hours and two minutes.

Postoperative course

The patient presented with postoperative bleeding in the first 24 hours which required a reintervention. He was subsequently discharged 10 days after surgery. One week after his discharge he was admitted due to a pericardial effusion and a sub-xiphoid pericardial window was performed. He was discharged yet again three days after. He is currently functional class I. On his most recent physical examination, cyanosis is absent, bilateral air entry is clear without crackles, S1 and S2 are audible with a regular rate and rhythm and no murmurs.

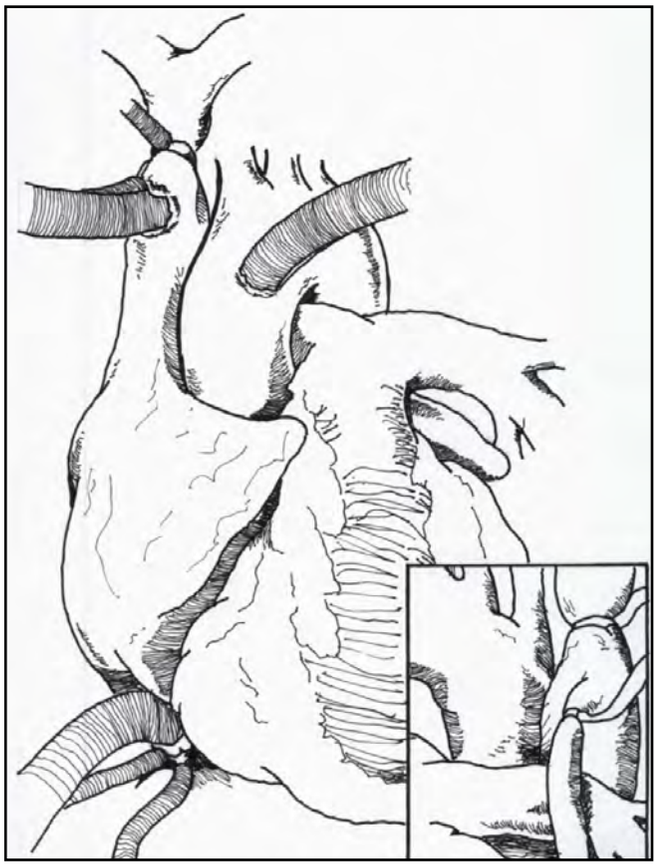

Figure 9. Aortic and bicaval cannulation, in preparation for cardiectomy.

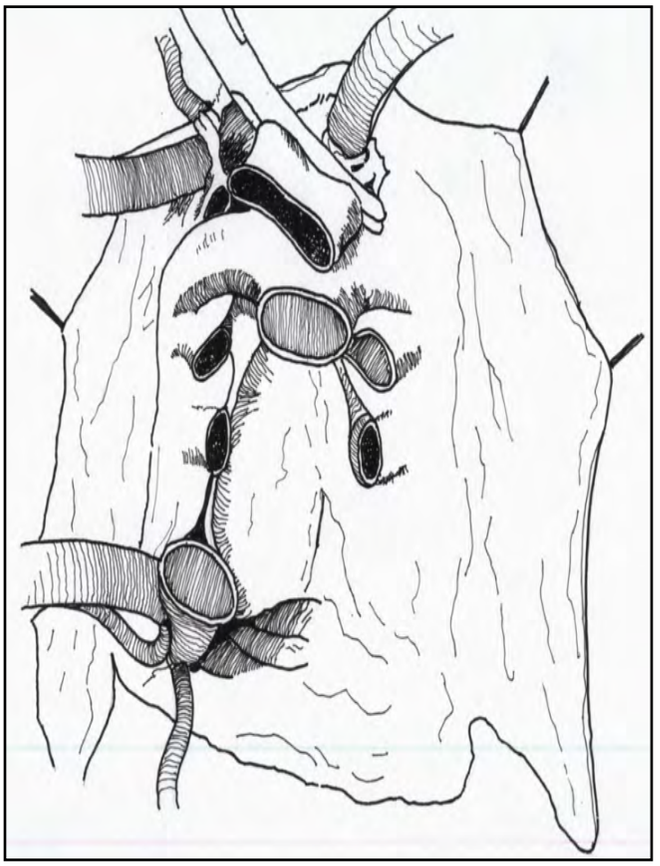

Figure 10. Complete cardiectomy (first part of the explant).

His immune suppression regimen includes Tacrolimus 1 mg every 12 hrs, aiming for levels between 11-14; Mycofenolate 1 mg every 12 hours; prednisone 12.5 mg daily with a progressive taper. His infectious prophylactic regimen consists of Trimethoprim/Sulfamethoxazole 160mg/800mg 1 tab daily from Monday to Friday; Valgancyclovir 450 mg daily; Itraconazole 200 mg daily. Blood testing and transthoracic echocardiography (November/2018) were normal. Spirometry (December 2018) FVC 4.48 (97%), FEV1 4.14 (107%). The most recent right heart catheterization (November/2018) had the following parameters: Pulmonary arterial pressure 11/4/8 mmHg, central venous pressure 1 mmHg and a pulmonary vascular resistance of 89. Endomyocardial biopsy did not reveal cellular rejection (ISHLT Grade 0R).

Morbidity and survival rates

The patient survival rate undergoing heart-lung block transplant has dramatically improved. Between 1982 and 1993 the survival rate average was two years, and in 2006 the survival rate was approximately 6 years **(Fig. 15) (Fig. 16)** [2]. It should be noted that there are some reports on a survival after surgery reaching up to 25 years [7]. The changes in survival rates are better appreciated over the last three eras of heart-lung block transplants **(Fig. 17).**

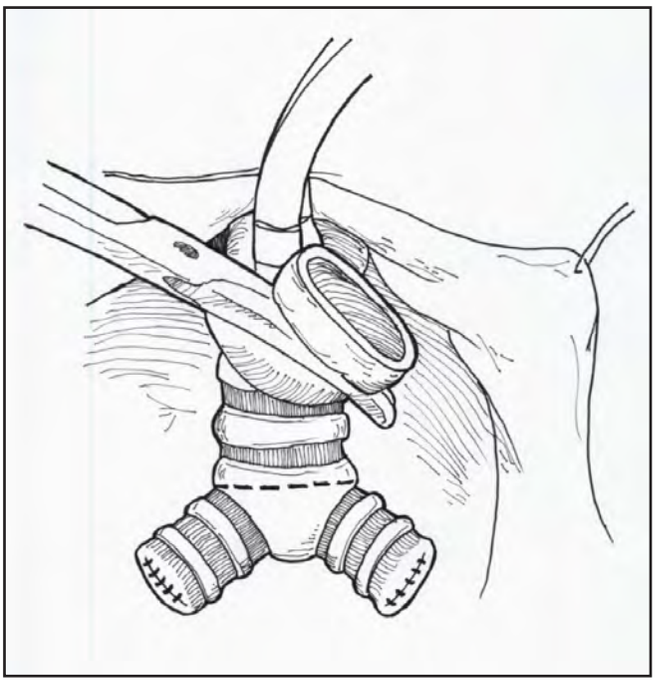

Figure 11. Traqueal division, in preparation to the anastomosis.

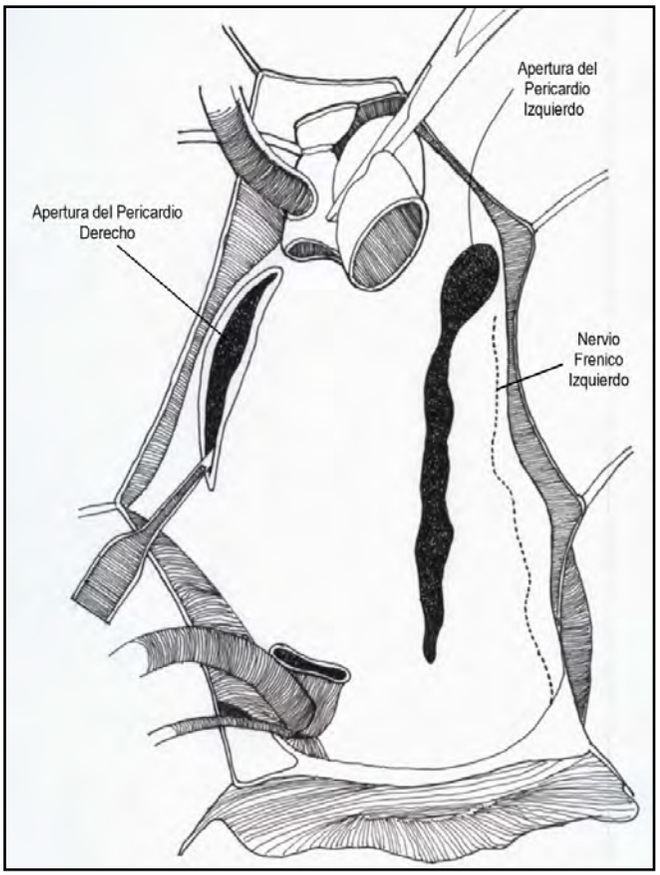

Figure 12. Pericardial incisions posterior to the phrenic nerves (opening for the insertion of the lungs).

The survival is lower in pacients with COPD than in cystic fibrosis **(Fig. 18)**. The first cause of mortality in the heart-lung transplant patiens, is infection or the primary graft dysfunction during the first year. After that, leading causes are bronquilitis obliterants and infection [2]**(Fig. 19)**.

The funcional class of the survivors is variable, in general, 30% are in class I after 3 years of follow-up **(Fig. 20) (Fig. 21)**. The most important complications at 5 years are: bronquilitis obliterans (31%), renal failure (13.7%), diabetes (27%) and cardiac allograft vasculopathy (7%) **(Fig. 22) (Fig. 23)**.

As in all the transplants, malignancy is a frecuent complication in the postoperative period. At 5 years, almost 10% will develop some kind of neoplasia **(Fig. 24) (Fig. 25).**

COMMENT

Heart-lung block transplant is currently a modality that is widely accepted for some patients with advanced and refractory cardiopulmonary disease. From the first operation in 1968, more than 2600 heart-lung block tranplants have been performed so far. The number of cases has declined in the last two decades partially due to an increase in bilateral lung transplantation [7]. Currently, the survival rate for a heart-lung block transplant is 70% at one year [2]. During the 90s decade, most of the multiorgan transplants that included lungs, were heart-lung blocks. Heretofore, most of the mutiorgan transplants continue to be heart-lung blocks. Although lung-liver, lung-kidney are more common to date, they are rather still scarce [2].

Generally speaking, survival rate for heart-lung transplants is similar to the one obtained for multi-organ trans-

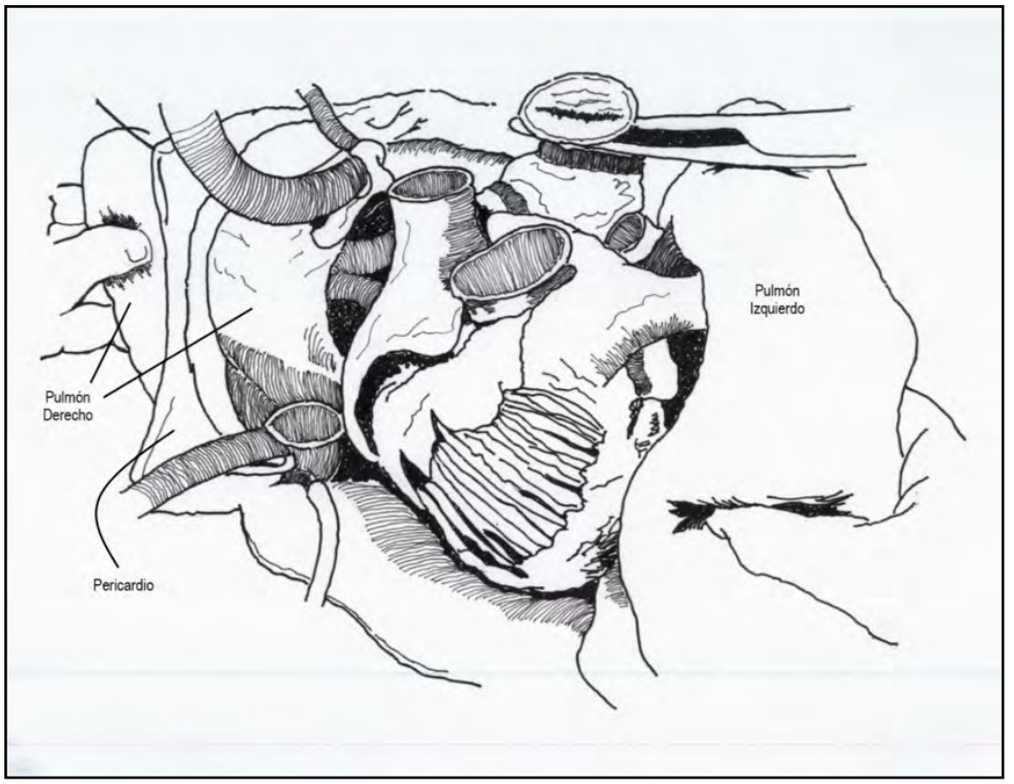

Figure 13. Heart-lung block placement: lung going inside the hemithorax across the pericardium

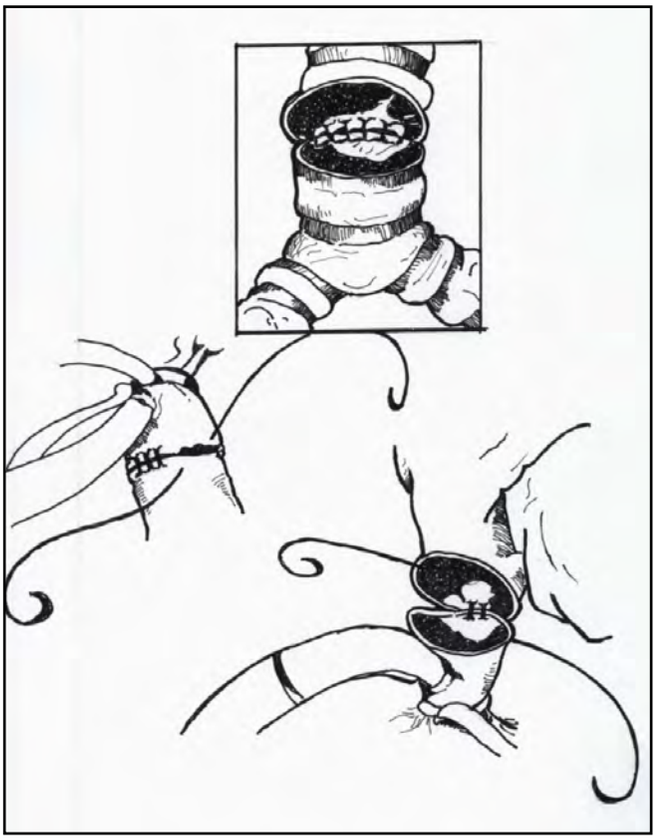

Figure 14. Tracheal and venae cavae anastomosis.

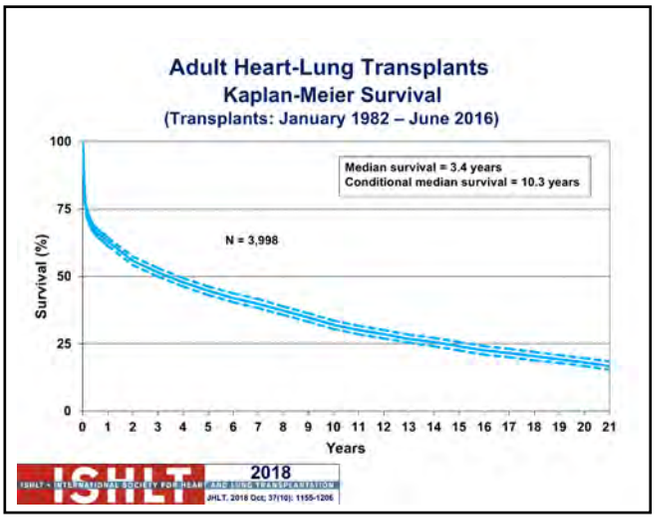

Figure 15. Survival calculated by the Kaplan-Meier method.
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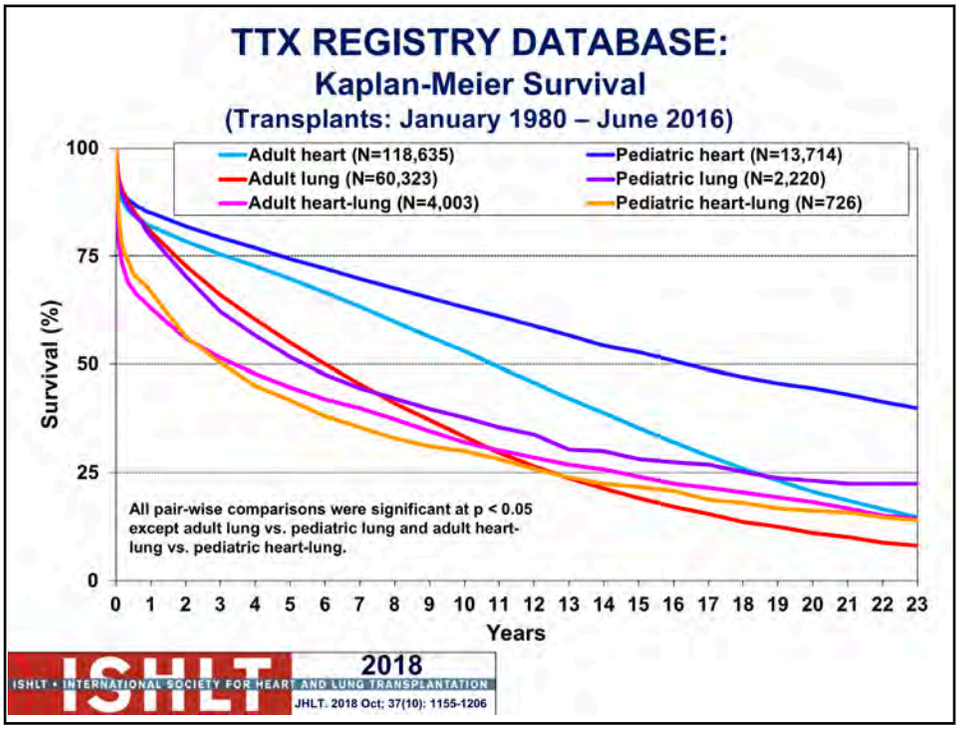

Figure 16. Survival calculated by the Kaplan-Meier method by groups.
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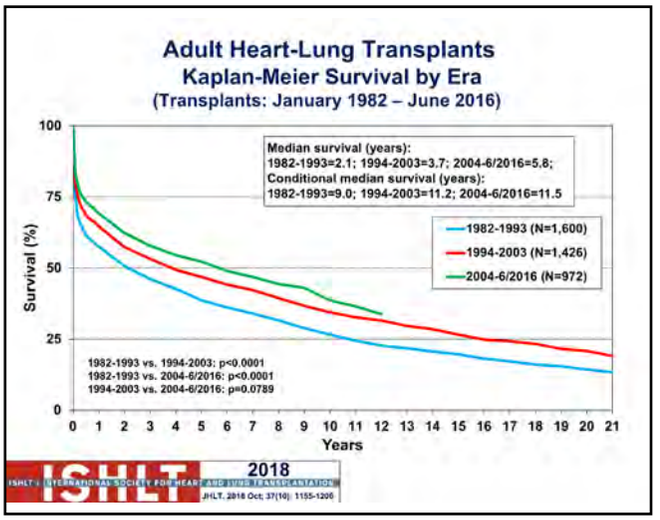

Figure 17. Survival calculated by the Kaplan-Meier method at different times.

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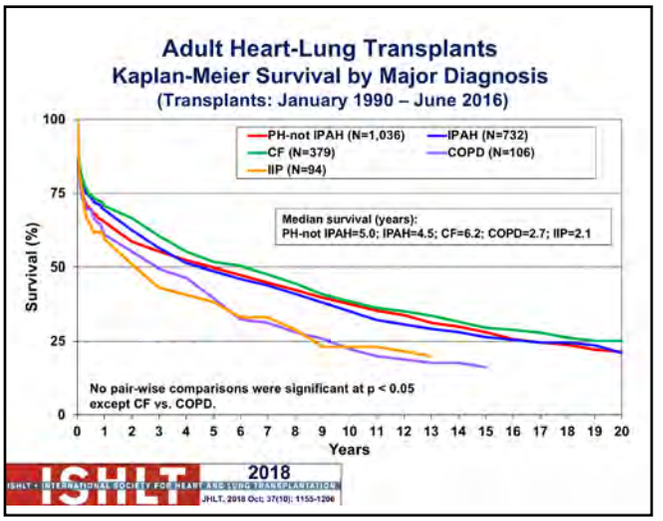

Figure 18. Survival calculated by the Kaplan-Meier method according to major diagnosis.

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plants. Causes for early postoperative mortality are due to graft failure (26.9%) and hemorrhage (23.5%). Our patient presented re-exploration for bleeding in the very early postoperative period, with a subsecuent good outcome. Complications and morbidity faced on with this kind of patients are multiple and complex, going from cardiac allograft vasculopathy to bronchiolitis obliterans, malignancy with skin cancer being the most frequent.

Adult-Heart Lung Transplants
Cause of Death (Deaths: January 1992 – June 2017)

CAUSE OF DEATH	0-30 Days (N=480)	31 Days - 1 Year (N=366)	>1 Year - 3 Years (N=297)	>3 Years - 5 Years (N=177)	>5 Years (N=561)
OB/BOS	0	14 (3.8%)	70 (23.6%)	38 (21.5%)	117 (20.9%)
Acute rejection	7 (1.5%)	8 (2.2%)	6 (2.0%)	1 (0.6%)	3 (0.5%)
Lymphoma	0	7 (1.9%)	12 (4.0%)	8 (4.5%)	12 (2.1%)
Malignancy, other	1 (0.2%)	8 (2.2%)	14 (4.7%)	7 (4.0%)	44 (7.8%)
CMV	0	2 (0.5%)	2 (0.7%)	1 (0.6%)	1 (0.2%)
Infection, non-CMV	81 (16.9%)	130 (35.5%)	84 (28.3%)	45 (25.4%)	117 (20.9%)
Graft failure	129 (26.9%)	76 (20.8%)	44 (14.8%)	32 (18.1%)	82 (14.6%)
Cardiovascular	39 (8.1%)	15 (4.1%)	22 (7.4%)	19 (10.7%)	55 (9.8%)
Technical	113 (23.5%)	12 (3.3%)	3 (1.0%)	3 (1.7%)	7 (1.2%)
Multiple organ failure	52 (10.8%)	54 (14.8%)	15 (5.1%)	7 (4.0%)	38 (6.8%)
Other	58 (12.1%)	40 (10.9%)	25 (8.4%)	16 (9.0%)	85 (15.2%)

Figure 19. Principal causes of death in heart-lung transplant recipients.

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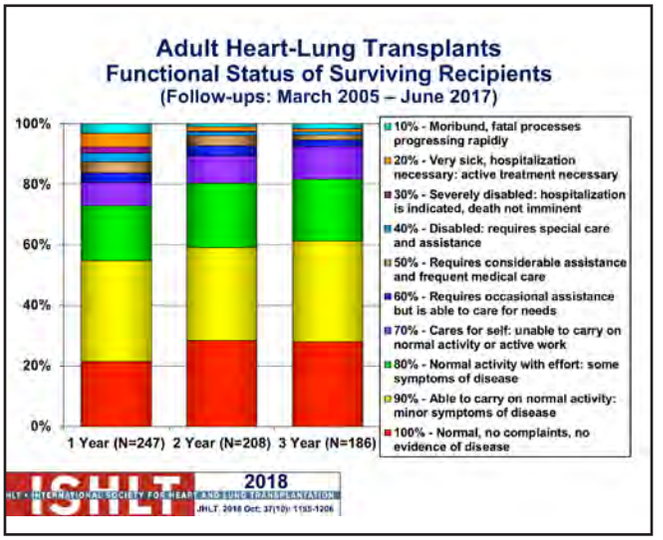

Figure 20. Functional status after heart-lung transplantation.

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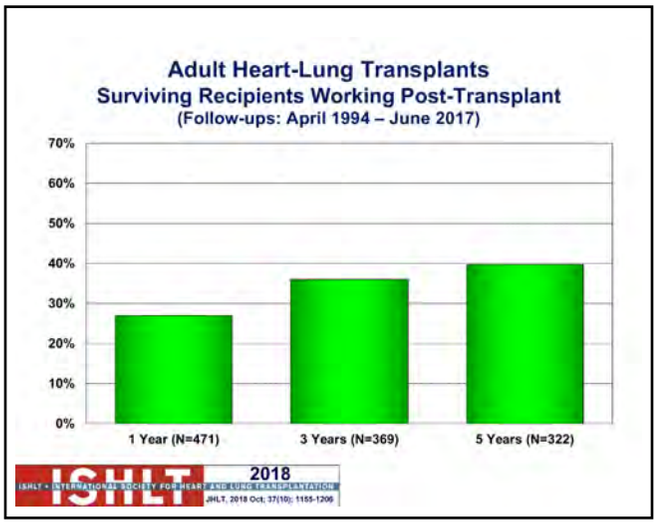

Figure 21. The employment status reported on annual follow-ups.
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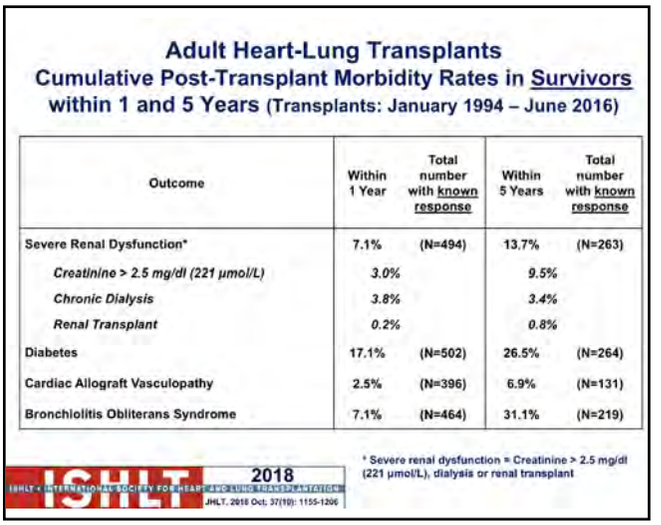

Figure 22. Morbidity observed in survivors between 1 to 5 years.
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Immunology for tranplants has tremendoulsy evolvelved from the first succesful reports of heart-lung block transplants at the beginning of the 80s. Nowadays, 80-90% of the pateints receive some type of pharmacologic therapy for induction, viz, generally IL-2R antagonists like Basiliximab or Daclizumab. Some cases have used thymoglobulin or OKT3 [13]. In 1980, the tipical regimen for immunesupression maintenance was based primarily on tacrolimus and mycophenolate. However, there are some groups that use combinations based

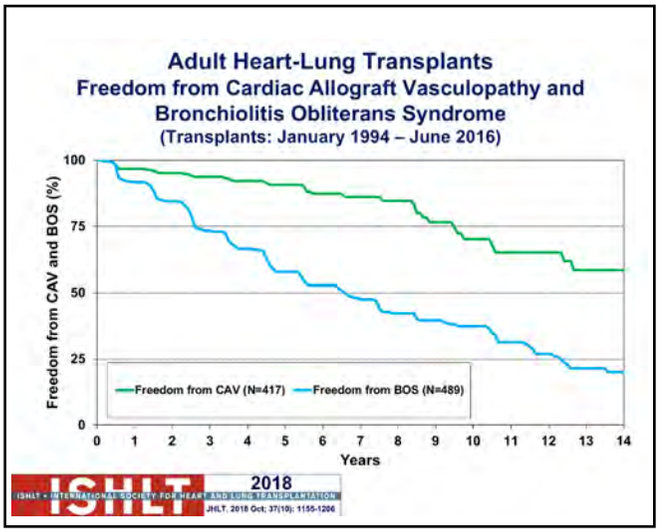

Figure 23. Freedom from cardiac allograft vasculopathy and bronchiolitis obliterans syndrome.
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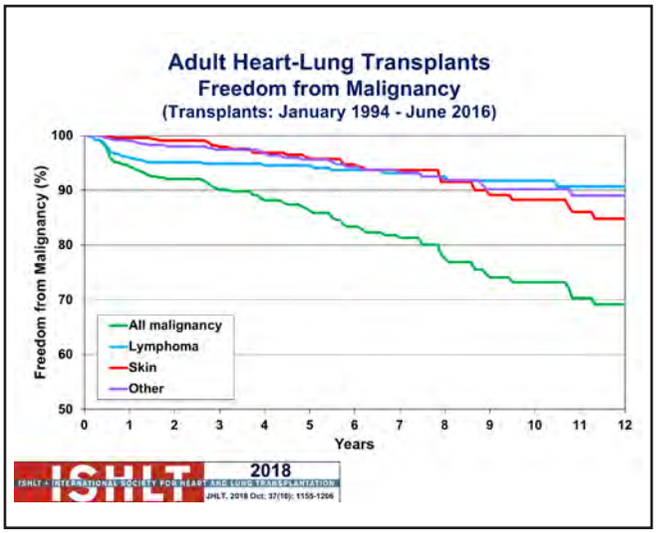

Figure 24. Freedom from malignancy.
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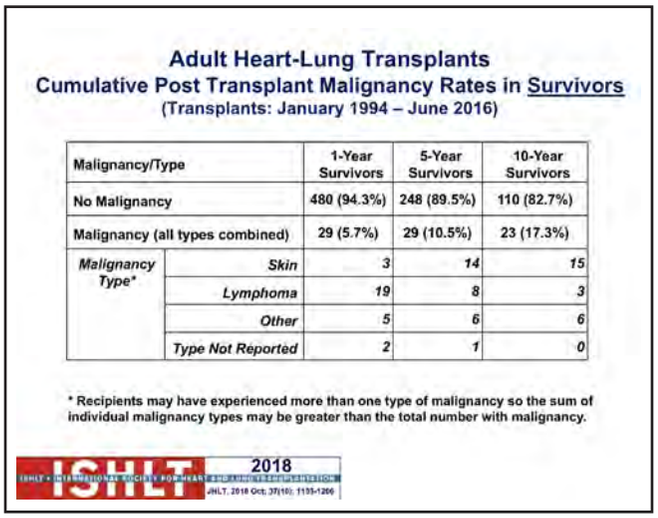

Adult Heart-Lung Transplants
Cumulative Post Transplant Malignancy Rates in Survivors
(Transplants: January 1994 – June 2016)

Malignancy/Type		1-Year Survivors	5-Year Survivors	10-Year Survivors
No Malignancy		480 (94.3%)	248 (89.5%)	110 (82.7%)
Malignancy (all types combined)		29 (5.7%)	29 (10.5%)	23 (17.3%)
*Malignancy Type**	*Skin*	*3*	*14*	*15*
	Lymphoma	*19*	*8*	*3*
	Other	*5*	*6*	*6*
	Type Not Reported	*2*	*1*	*0*

* Recipients may have experienced more than one type of malignancy so the sum of individual malignancy types may be greater than the total number with malignancy.

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Figure 25. Cumulative post-transplant malignancy rates in survivors.
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on aziathropine, cyclosporine and/or sirolimus [7].

The data mentioned in this revision coming from the 35th report of the International Society for Heart and Lung Transplant serves as a guide to make safer, easier the decision-making process with regards multiorgan transplant in a difficult patient population. The scarcity of donors has always been the Aquiles tendon for transplantation, with thoracic organs not being the exception. In the past, it has been described to perform a "domino" procedure, where the recipient needs a bilateral lung transplant, but with a heart free from disease. Thus, the heart is explanted and transplanted to an adequate recipient with primary cardiac disease simultaneously with the first patient receiving the heart-lung block with the procurment technique mentioned above [5]. In this report we describe with precision the diverse surgical techniques involved in this procedure, going from procurement and the recipient explant to the heart-lung block implant. The procedure is technically feasible, accesible, and reproducible. Even knowing that the lack of donnors is the key and crucial point for an expansion in the surgical techniques for transplant, the vision and clinical/surgical perspective must originate always at the basis of an incessant search for progress. This leads ultimately to radical changes in each and every aspect to the these complex patients.

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