Case Report

Development of a Non-Heart-Beating Lung Donor Program With «Bithermia Preservation», and Results After One Year of Clinical Experience

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A R T I C L E   I N F O

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A B S T R A C T

The number of lung transplantations that are performed in Spain continues to grow, with 235 transplant recipients in 2010. Non-heart-beating (NHB) donations have contributed to this upward progression. Our Lung Transplant Unit began its activity in October 2008 and during these last three years 97% of the transplant interventions performed have been successful. In order to increase the number of donations, we have developed a NHB donor program as part of the existing organs program in our hospital. In doing so, the development of a multi-organic preservation method (lung, liver and kidney), which we call «Bithermia Preservation», was necessary. This paper presents this methodology as well as the first year of clinical application experience. During this time, 3 patients have been transplanted using such NHB donations. None of them developed primary graft dysfunction (PGD); all the patients have been discharged and lead active lives without any evidence of bronchiolitis obliterans syndrome.

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Desarrollo de un programa de donación pulmonar en asistolia con «preservación en bitermia» y resultados tras un año de experiencia clínica

R E S U M E N

El número de trasplantes pulmonares que se realizan en España continúa en ascenso, con 235 pacientes trasplantados en 2010. Los programas de donantes en asistolia han contribuido a esta progresión. Nuestra Unidad de Trasplante Pulmonar comenzó su actividad en octubre de 2008, y en estos 3 años se han trasplantado con éxito el 97% de los pacientes intervenidos. Para obtener un mayor número de donantes hemos desarrollado un programa de donación pulmonar en asistolia a partir del programa existente en nuestro hospital. Fue necesario la elaboración de una metodología de preservación multiorgánica (pulmonar, hepática y renal) que hemos denominado «preservación en bitermia». Presentamos la experiencia de su aplicación clínica durante el primer año. Hemos trasplantado 3 pacientes utilizando este tipo de donantes en asistolia. Ninguno de los pacientes desarrolló disfunción primaria del injerto, todos fueron dados de alta, realzan vida activa y sin datos de síndrome de bronquiolitis obliterante.

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Introduction

Brain death donors represent the majority of solid organ transplant donors. In the last decade, given the need to increase the number of multiple-organ donors in order to cover transplant necessities, alternatives to conventional donors have been developed, such as donors in cardiac arrest (non-heart-beating (NHB) donors), including both in-hospital (controlled) as well as out-of-hospital (uncontrolled).

As for lung transplantation, asystolic donation is a field that has been extensively researched over the last decade. It is supported by the hypothesis that lung tissue can be viable after the death of the organism and that these lungs can be valid for transplantation, even if they are extracted a considerable time after death.¹ Furthermore, after the death of the organism, lungs have been demonstrated to continue to be viable as it has been observed that pulmonary epithelial cells can be cultivated from samples obtained from cadavers.²

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With the aim to demonstrate this hypothesis, innumerable experimental studies have been developed. One of the aspects analyzed has been the effect of warm ischemia time from the time of the cardiac arrest until the organ preservation maneuvers. It has been seen, for example, that after 2 h of warm ischemia and without the need for pulmonary circulation, it is possible to obtain adequate gas exchange. This safe period of warm ischemia could be increased up to 4 h if the donor were heparinized, while topical cooling is the best method of preservation for non-ventilated lungs, reaching preservation periods of up to 12–24 h.

Based on these advances, the first clinical lung transplantations were carried out with organs from in-hospital NHB donors. In Spain over the course of the last 15 years, programs have been developed with out-of-hospital NHB donors, successfully obtaining renal, hepatic and tissue grafts. In order to do so, a donor preservation method is used until consent is obtained for organ extraction; it is based on extracorporeal membrane oxygenation (ECMO), which can be in normothermia or in deep hypothermia, depending on whether the liver is going to be used. After 2002 in Madrid, thanks to the collaboration with one of these NHB programs that use ECMO in deep hypothermia, lung grafts that had been preserved with topical cooling of the pleura started to be successfully used.

The Lung Transplantation Unit at the Hospital 12 de Octubre started its activities in 2008. As of October 2011, we have performed 37 lung transplantations, with a hospital mortality of 2.7% (one patient), a 94% one-year survival and an 87% three-year survival. Currently, according to the Spanish National Transplantation Register, our group has the best survival results compared with other Spanish lung transplantation groups that have an overall one-year survival of 71% and a three-year survival of 59%.

With the need to obtain a greater number of donors and encouraged by the existence in our hospital of a program of out-of-hospital NHB donors directed at obtaining abdominal organs (liver and kidneys) and tissues, we considered the possibility of evaluating the lung grafts from these donors. We thus developed a project with the following objectives:

- To carry out lung preservation maneuvers in the NHB donors until family and judicial consent was obtained for the extraction.
- To analyze the lung function in order to validate the lung grafts.
- To extract and implant the grafts that were considered valid.

The main objective was to increase the number of possible lung donors of transplants and, secondly, to increase our understanding of NHB lung donation.

**Clinical Observations**

The project started by defining the inclusion and exclusion criteria specific to NHB donation.

**Inclusion Criteria**

- Age ≤55
- Known cardiac arrest time
- Resuscitation begun within 15 min of the cardiac arrest
- Normal chest X-ray
- Maximum time transpired from arrest to topical cooling of the pleura: 180 min
- Maximum lung preservation time: 240 min

**Exclusion Criteria**

- The same criteria for brain-death donor with regard to medical history and serology

![Fig. 1. Two pleural tubes in each hemithorax in order to recirculate the cool preservation solution.](image)

- Major cranioencephalic trauma with loss of encephalic mass

One of the differential aspects of our program is that the preservation of the abdominal organs is done by means of ECMO in normothermia, unlike other programs that use deep hypothermia. This made us design a recirculation system for the pleural preservation solution in order to maintain topical cooling and avoid warming of the lungs. We have come to call this multiple organ preservation methodology for NHB donation “bithermia preservation”, as the abdominal normothermia coincides with the thoracic hypothermia.

The process initiates when the hospital transplantation coordinators advise us about the arrival of a possible NHB donor. At this time, a team goes to the hospital to carry out lung preservation maneuvers. Once the patient enters the OR, while the femoral vessels are cannulated for the ECMO and the donor is maintained with cardiac compression, bronchoscopy is carried out and a bronchial aspirate sample is taken for culture. After the femoral artery cannulation, 300 ml of venous blood is obtained from the donor, which is kept in a heparinized bag at room temperature. Once in ECMO, the cardiac compressor is withdrawn and the mechanical pulmonary ventilation is disconnected. Afterwards, lung preservation maneuvers are performed. Two apical pleural drains are placed, one on each side, in order to introduce the cold preservation solution (Perfadex®), and another two basal drains are inserted in order to let the solution drain out. These four tubes are connected to a closed circuit that enables the solution to move through the pleural cavities (Fig. 1). This solution is recirculated thanks to a roller pump and it is cooled to 4 °C by means of a cardioplegia delivery system and heat exchanger. The temperature is controlled with a thermometer at the pleural outlet of the preservation circuit.

Once the consents are obtained, sternotomy is performed and the lung function is evaluated using a bag of venous blood from the donor. In an experimental study, we confirmed the validity of this methodology for lung function evaluation, identifying in addition the need to continue using blood for the correct determination of pulmonary oxygenation avoiding the use of Perfadex® solution as the pulmonary fluid. Afterwards, the lung extraction is carried out in the usual manner.

We established criteria for considering the lung graft as valid, which were:

- Normal chest radiograph
- Compliance with the established time limits
- Bronchoscopy with no findings of bronchial aspiration, pulmonary edema, important purulent or hematic secretions, or airway lesions
• Normal pulmonary macroscopic evaluation
• Negative viral serology
• Gases obtained in the left auricle and pulmonary veins >400 mmHg

Afterwards, the extraction was continued in the same manner as in conventional donors, and the implant was done in accordance with the standard technique.

We established a preclinical project development period in order to assess its viability as well as its influence on the renal and hepatic transplantation programs. During the preclinical phase of the program, 17 donors were assessed in 8 of whom chest radiography was normal (47%) and bronchoscopy was normal in 9 (52%). We performed lung preservation maneuvers in 12 donors. In 85% of the donors (6/7), no soft tissue edema was observed during the apertures, and in 57% of the donors (4/7) in whom lung function evaluation was done the gases obtained were valid.

With these results, we decided to initiate the clinical phase. We performed the first lung transplantation with an out-of-hospital NHB donor using “bithermia preservation” in June 2010 in a 49-year-old patient with alpha-1 antitrypsin deficiency. We successfully carried out bilateral lung transplantation with excellent lung function after more than 12 h of total ischemia. Since then, between June 2010 and July 2011, we have assessed 15 NHB donors. The chest radiography was normal in 6 donors (40%) (Fig. 2), 7 donors presented with pulmonary infiltrates, in one the radiography was of poor quality and in another it could not be done. Bronchoscopy was normal in 8 donors (53%), 3 presented abundant hematic secretions in the airway and in 2 there were findings of bronchial aspiration.

Lung preservation maneuvers were done in 6 donors. One donor was ruled out due to starting with hematic secretions during the preservation time, and in another there was no matching recipient. The lung function assessment was done in 4 donors, and the gases obtained were adequate in 75% of the cases (3/4). Three lung transplant donors, aged 38, 41 and 54, were considered valid; therefore, we carried out 3 lung transplantations: one bilateral and 2 unilateral. We offered 2 lung grafts to the National Transplant Organization (NOT) for other lung transplantation groups. The characteristics of the transplant recipients, the type of transplantation done and the post-op evolution are shown in Table 1. None of the transplants presented with primary graft dysfunction (PGD), and the three showed excellent lung function which led to early extubation in 2. There was no hospital mortality. The long-term evolution is shown in Table 2. The 3 patients are alive, none of them have presented bronchiolitis obliterans syndrome and they are living active lives.

**Table 1**

Characteristics of the Transplant Recipients, Type of Transplant and Post-op Evolution.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Indication</th>
<th>Type of Transplant</th>
<th>Ischemia Time</th>
<th>pO₂/FiO₂ Arrival RU</th>
<th>Extubation, h</th>
<th>Exitus Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>49</td>
<td>Emphysema α1AT def</td>
<td>Bilateral</td>
<td>12 h 40 min</td>
<td>243</td>
<td>120</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>62</td>
<td>Emphysema</td>
<td>Unilateral, right</td>
<td>11 h 15 min</td>
<td>391</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>64</td>
<td>Emphysema</td>
<td>Unilateral, left</td>
<td>11 h 44 min</td>
<td>402</td>
<td>4</td>
<td>No</td>
</tr>
</tbody>
</table>

α1AT def: alpha 1 antitrypsin deficiency; RU: resuscitation unit.

**Table 2**

Long-term Evolution of the Transplant Recipients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Acute Rejection Episodes</th>
<th>BOS</th>
<th>Survival, Months</th>
<th>Alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>No</td>
<td>15</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td>No</td>
<td>6</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>No</td>
<td>4</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Discussion**

The first solid organ transplants came from NHB donors. Currently, with the increased indication for transplantation there is a new interest in this type of donors. While in other countries NHB donation is mainly limited to controlled donors, in Spain the donors are mostly uncontrolled. This was influenced by the development of Spanish legislation regarding organ donation, the collaboration of out-of-hospital emergency units and the NTO in the development of these programs.

In Spain, lung transplantation using out-of-hospital NHB donors has been a consolidated reality since 2002, and Madrid is the world-wide pioneering city in this activity. Until now, the type of organ preservation used in these multiple-organ donors consisted of establishing ECMO in deep hypothermia (4 °C) in order to obtain renal grafts (the liver transplantation results with hypothermia were not good) and topical pleural cooling in order to obtain lung grafts, or instead ECMO in normothermia to obtain hepatic and renal grafts. With the development of the “multiple organ bithermia preservation” method, we have been able to successfully use kidney, liver and lung grafts from the same NHB donor.

As for the out-of-hospital NHB donors that we have evaluated, we have observed that the information from chest radiography is important and was able to identify pulmonary pathology in half of the cases. It is likely that the processes that accompany cardiac arrest, such as arrhythmias and heart failure, may condition the appearance of cardiogenic pulmonary edema. Likewise, bronchoscopy provides a lot of information regarding the presence of bronchial aspiration and hematic secretions that invalidate the graft as being apt for transplantation.

The incidence of edema in the soft tissues of the NHB donor in our program was very low. This is influenced by the strict management of the extracorporeal membrane circulation done by the perfusionist, who is present during the entire preservation process, by avoiding excessive volume and by doing an ultrafiltration process when necessary.

In our experience, with “bithermia preservation” we obtain sufficient pleural hypothermia for proper lung preservation. In donors

![Fig. 2. Chest radiography of a valid non-heart-beating donor.](image-url)
with chest X-rays showing no lung alterations, with normal bronchoscopy who do not develop problems during this preservation time, excellent oxygenation parameters are obtained in 75% of cases (pO2/FIO2 >400 mmHg).

As for the initial postoperative evolution, we highlight that none of the 3 lung transplants developed PGD. The advantages of the NHB donors over conventional donors are that they do not experience the pulmonary effects of brain death (neurogenic pulmonary edema) and that there is a short mechanical ventilation time. The references of other authors of a greater incidence of PGD in lung transplants from NHB donors\(^\text{16}\) are not shared by our group. It is striking that, in our program, despite having increased the warm ischemia time (from cardiac arrest until lung cooling) to 3 h compared with the 2 h of other groups, we have not observed greater graft dysfunction. In this regard, we believe that proper donor selection is fundamental and all inclusion and exclusion criteria should be met.

The results of the lung transplants done by our group confirm the validity of the “bithermal preservation” procedure, and they establish the possibility of performing multi-organ extraction (kidneys, liver and lungs), which increases the cost-effectiveness of NHB donors.

In the future, we may possibly assess exsanguinated NHB donors or those with hemorrhagic lesions, in whom the abdominal organs would be rejected, and only lung preservation maneuvers would be done.

Acknowledgements

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References