Arch Bronconeumol. 2016;52(12):596–604

Sociedad Española de Neumología y Cirugía Torácica SEPAR

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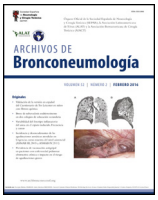

Review

Technical Aspects and Benefits of Experimental Mouse Lung Transplantation☆

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ARTICLE INFO

Article history:
Received 4 February 2016
Accepted 15 April 2016
Available online 1 November 2016

Keywords:
Transplantation
Mouse model
Experimental
Lung

ABSTRACT

In recent years, the number of lung transplantations performed as the last option for many respiratory diseases has grown considerably, both in adults and children. However, the causes for the relatively short survival of lungs compared to other organ transplants still need to be studied.

Techniques have improved since the 1950s when experimental lung transplantation began, and the different animal species used now include rodents. The advantage of using these small species is that the surgical model has been expanded and standardized, and different respiratory problems can be studied.

In this review we examine the different technical strategies used in experimental transplantation in rats and mice, focusing on surgical techniques and anesthesia and monitoring methods, and highlighting the major contributions of mouse lung transplantation to the field.

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Aspectos técnicos y utilidades del trasplante pulmonar experimental murino

Palabras clave:
Trasplante
Modelo murino
Experimental
Pulmón

RESUMEN

A lo largo de las últimas décadas, el número de trasplantes pulmonares realizados como terapia final de muchas enfermedades respiratorias ha ido creciendo considerablemente, tanto en la población adulta como a nivel pediátrico. Sin embargo, se hace muy necesario estudiar las causas por las que su supervivencia es relativamente baja en comparación con otros trasplantes de órganos.

Por ello, desde mediados del siglo pasado comenzaron a realizarse trasplantes pulmonares experimentales, cuya técnica ha ido mejorando, y se ha ampliado a distintas especies animales hasta llegar a los roedores. La ventaja que presentan estas especies pequeñas ha facilitado que el modelo quirúrgico se haya extendido y estandarizado, permitiendo estudiar diferentes aspectos relacionados con las enfermedades respiratorias.

En esta revisión se analizan las distintas modalidades técnicas disponibles de trasplante experimental en rata y ratón, destacando tanto la técnica quirúrgica como la anestésica o la monitorización, así como las principales aportaciones generadas por el trasplante pulmonar murino.

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Introduction

Lung transplantation is occasionally the only therapeutic option available in the final stages of respiratory diseases such as chronic obstructive pulmonary disease, diffuse interstitial pulmonary disease, bronchiectasis associated with cystic fibrosis, bronchiolitis obliterans, sarcoidosis or arterial pulmonary hypertension.[1–3]

Since the first transplantations were performed in animals in 1940,[4,5] these experimental models have contributed to the development of surgical procedures and the prevention of associated complications, such as rejection or ischemia–reperfusion injury. Although the first mouse transplantation took place in 1971,[6] in the 20th century the procedure was generally performed in dogs,[4,5] pigs, sheep[7] and monkeys,[8–10] since larger animals offer

☆ Please cite this article as: Ruiz-Pérez D. Aspectos técnicos y utilidades del trasplante pulmonar experimental murino. Arch Bronconeumol. 2016;52:596–604.

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advantages in the development of surgical techniques and transfer of results to humans in the clinical setting. These species continue to be used today, particularly for surgical training, but smaller species, such as rabbits,[11] rats and mice, which have considerable advantages in terms of expense, management and logistics, and are less constrained by ethical considerations, have acquired greater prominence.

Orthotopic transplantation of the left lung was initially developed in rat models,[6] while heart–lung transplant is less common due to high mortality rates.[12] Improvements in surgical and anesthetic techniques, mechanical ventilation and preservation and reperfusion of organs have improved the success rate and reproducibility of the model. Heterotopic transplantation models have also been developed, although ventilation and good graft perfusion have not been achieved.[13,14] Finally, the mouse model is enhanced by the availability of a wide range of strains that allow the study of genetic factors that may affect the transplant.[15,16]

The aim of this review is to describe the different procedures used in mouse lung transplantation, paying special attention to surgical techniques and perioperative management, including anesthesia–analgesia, mechanical ventilation, post-operative care, and prevention of complications. We also review the main clinical contributions of lung transplantation in rodents.

Anesthesia and Perioperative Care

Anesthetic protocols must provide sufficient anesthesia and analgesia to maintain the physiological stability of the animal, and they must be easily reversible after surgery is completed. Although induction and recovery from inhalation anesthesia[16] (1.5%–2% isoflurane or 2.5%–3% sevoflurane, both known to protect the lung[17]) is rapid, this technique can be difficult to apply in the absence of proper facilities. Specifically, considerable economic resources are called for, as inhalation anesthetics are costly, and a team specializing in mechanical ventilation must be available to administer the anesthetic gases. When inhalation anesthesia is not an option, parenteral methods can be used instead (Table 1).

Ketamine is one of the most widely used drugs. It provides an analgesic effect which is enhanced when administered together with an α2-adrenergc receptor antagonist, such as xylazine or medetomidine, which simultaneously reduces muscle rigidity. This combination of anesthetics can be easily reversed with the administration of an α2-adrenergic receptor antagonist, such as atipamezole. Other combinations include ketamine and the benzodiazapine diazapam, or fentanyl combined with medetomidine.

Diuresis caused by α2-adrenergic receptor antagonists must be compensated with subcutaneous fluid replacement. Ophthalmic ointment must also be applied to prevent corneal dryness.

Thoracotomy is a potent nociceptive stimulus, so appropriate analgesia is essential. Analgesia is generally provided in the form of preoperative subcutaneous administration of opioids (e.g., buprenorphine, 10–50 μg/kg/8 h in rats or 50–100 μg/kg/8 h in mice) combined with non-steroidal anti-inflammatory drugs (meloxicam 2 mg/kg/day). Finally antibiotic prophylaxis with cefazolin (30 mg/kg) or ceftriaxone (70 mg/kg) is recommended.

Ventilation

Once anesthetized, the animals must be intubated with 14 G catheters for rats >300 g, 16 G for rats 200–300 g or 22 G for mice weighing around 25 g, and mechanically ventilated. For the recipient, the pressure-controlled mode is usually recommended, since the left lung will not be functional during a large part of the surgery.

The ventilator should be set to a tidal volume of 7–10 ml/kg (if volume-controlled ventilation is used), or a maximum pressure of 10–12 cm H_2O (in the case of pressure-controlled ventilation), with a respiratory rate of 60–100 breaths/minute. Moreover, a positive end-expiratory pressure of 2–5 cm H_2O is highly recommended for avoiding the formation of atelectasis during expiration.

Intraoperative Monitoring

Equipment specifically designed for rodents is available for recording pulse oximetry, capnography, non-invasive arterial pressure or electrocardiogram. Devices designed for humans or large animals are generally unsuitable for rodents.

It is also important to monitor body temperature using a thermometer or rectal probe and to maintain it between 37.5 and 38.5 °C. Hypothermia is a very common complication in rodents and adverse events can occur if temperatures fall below 32 °C, including delayed recovery from anesthesia. An electric blanket or hot water bottle can be used to maintain body temperature, although the animal must be monitored to avoid possible hyperthermia. Oxygen saturation tends to remain at levels above 99% when the inspired fraction of oxygen is increased to between 30% and 60%, compared to 21% ambient air.

Surgical Aspects of Orthotopic Lung Transplantation in Mice and Rats

The left lung orthotopic transplantation model is the most widely used, thanks to its viability and greater simplicity, since the left lung is formed of a single lobe, while the right lung is divided in 4. However, orthotopic transplantation of the right lung has also been performed in mice.

Preparation of the Donor

Extraction of the complete heart–lung block is generally recommended. The animal is anesthetized and placed in a supine

Table 1
Anesthetic Combinations Used in Rats and Mice During Surgical Procedures, Including Lung Transplantation.

Protocol	Dose (mg/kg)		Duration (min)
	Rat	Mouse	
Ketamine + medetomidine	75–100 + 0.25–0.5	75–150 + 0.5–1	40–50
Ketamine + xylazine	75–100 + 12	75–150 + 12–20	40–50
Ketamine + diazepam	80 + 20	75–100 + 5	30–40
Medetomidine + fentanyl	0.3 + 0.3	–	50–60
Atipamezole[a] (α2-adrenergic antagonist)	0.5–1	0.5–1	–

[a] Medetomidine and xylazine can be blocked with atipamezole.

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