Donor Type Impact on Ischemia-Reperfusion Injury After Lung Transplantation

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Background. **Extended criteria donors, non–heart-beating donors (NHBD), and living donation are options to overcome the organ shortage for lung transplantation (LTx). However little is known about the impact of the donor lung on ischemia-reperfusion injury (IRI), which often leads to high mortality rates.**

Methods. **Recipient pigs (N = 32) were divided equally into 4 groups according to their donor status: (1) living donor = control group, (2) conventional heart-beating donor, (3) non–heart-beating donor according to Maastricht category I (NHBD-I), and (4) Maastricht category IV (NHBD-IV). After cold flush and 3 hours of hypothermic preservation, a single left LTx was performed. Thereafter only the transplanted left lung was ventilated and perfused to assess isolated left lung function at 1 and 2 hours after LTx compared with before LTx.**

Results. **No significant differences were seen between the 4 groups regarding wet-to-dry weight ratio, mean airway pressure, or compliance. Arterial oxygenation and alveolar-arterial difference showed significant differences between the groups ($p < 0.05$). Two-way analysis of variance (ANOVA) for the factors brain death and cardiac arrest found significantly increased alveolar-arterial differences for the brain-death group but not for the beating-heart donor group.**

Conclusions. **The use of lungs from brain-death donors and NHBDs has different effects on the occurrence of symptoms of IRI after LTx. Further observations and therapeutic strategies are necessary to minimize IRI when grafts from NHBDs are used.**

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Lung transplantation (LTx) has developed into a successful therapy for patients with end-stage pulmonary disease that is refractory to medical treatment [1]. The shortage of organ donors, however, leads to an increased loss of patients on the waiting list. Additionally, LTx outcome is hampered by reduced graft function from ischemia-reperfusion injury (IRI) [2, 3], with 3-month mortality rates of 28% [1]. IRI is characterized by nonspecific alveolar damage, lung edema, and hypoxemia, which usually occur within 72 hours after LTx.

To overcome the problem of a donor shortage, new strategies have been sought to increase the pool of lung donors, including the use of lungs after cardiac arrest of the donor [4]. In contrast to the kidney or the heart, the lung is less vulnerable to the effects of hypoxemia after cardiac arrest because of its oxygen reservoir in the alveoli [4]. Several groups have started transplanting lungs from non–heart-beating donors (NHBD) of controlled and uncontrolled Maastricht categories I to IV [5], and the first data have been promising that such lungs can achieve good pulmonary function [6–8].

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However important questions remain to be answered, such as whether ischemia after cardiac arrest aggravates ischemia-reperfusion injury (IRI) and contributes to primary graft dysfunction. Experimental LTx models have been shown to be useful for assessing graft function after cardiac arrest [9–11]. Hence in this study we used a porcine LTx model to determine the impact of brain death and cardiac arrest on early signs of IRI in the transplanted lung.

Material and Methods

Experimental Groups

Animals received human care in compliance with the Principles of Laboratory Animal Care formulated by the National Society for Medical Research and the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIH publication no. 86–23, revised 1996). The study was approved by the Ethical Committee for Animal Research at the University of Leipzig.

Pathogen-free pigs (N = 32; body weight: 38 to 48 kg) were randomly assigned in equal numbers to 4 groups (Fig 1): (1) control group receiving grafts of living donor (LD) animals; (2) conventional brain-dead heart-beating donor (HBD); (3) uncontrolled non–heart-beating donor of Maastricht category I (NHBD-I); and (4) controlled non–heart-beating donor of Maastricht category IV, in

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Abbreviations and Acronyms

CA	= cardiac arrest
DLC	= dynamic lung compliance
ECG	= electrocardiogram
h	= hour
HBD	= heart-beating donor
IRI	= ischemic reperfusion injury
IU	= international units
LD	= living donor
LTx	= lung transplantation
Min	= minute
NHBD	= non–heart-beating donor
NHBD-I	= non–heart-beating donor according to Maastricht category I
NHBD-IV	= non–heart-beating donor according to Maastricht category IV
$PaCO_2$	= partial pressure of carbon dioxide
Pao_2	= partial pressure of oxygen
PAP	= pulmonary artery systolic pressure
SAP	= systolic arterial blood pressure
SD	= standard deviation

which cardiac arrest succeeded brain death (NHBD-IV). General parameters, such as body weight, were comparable between the groups.

Surgical procedures, donor and recipient procedures, and donor lung procurement were performed as previously described [12].

Donor Procedure

Anesthesia, induced with an intramuscular injection of Stresnil (alprazolam) 0.4 mg/kg (Azaperon, Janssen-Cilag, Neuss, Germany) and ketamine 0.2 mg/kg/body weight (BW), (Ursotamin, Serumwerk Bernburg, Bernburg, Germany), was maintained with Dormicum (midazolam) 0.2 mg/kg/BW (Midazolam, Ratiopharm, Ulm, Germany), Trapanal (thiopental) 4 mg/kg (Thiopental-Natrium, Nycomed, Konstanz, Germany), and fentanyl 0.5 mg/kg/hour (Fentanyl, Janssen-Cilag, Neuss, Germany). Intravenous relaxation was achieved with pancuronium bromide (Ratiopharm, Ulm, Germany). The animals were ventilated (Titus, Draeger, Germany) with an inspiratory oxygen fraction (FIO_2) of 1.0, a tidal volume of 8 mL/kg, a frequency of 20 breaths/min, and a positive end-expiratory pressure of 5 cm H_2O. A femoral artery catheter (2.7 F, Vygon, Ecouen, France) was used for measurements and blood sampling. A central venous line in the right internal jugular vein measured the central venous pressure.

After baseline hemodynamic measurements were obtained, a median sternotomy was performed and the pulmonary artery, ascending aorta, and caval veins were encircled. Heparin 300 IU/kg was administered for systemic anticoagulation. (B. Braun Medical, Germany). The pulmonary artery was cannulated and isolated from the ascending aorta.

Brain death was initiated with a subdurally placed balloon (10F, Norta Latex Plus, BSN Medical, Hamburg, Germany) after trepanation of the frontal bone [13]. Hemodynamic changes, associated with the catecholamine storm (Cushing's response), were observed and documented. After attenuation of Cushing's phenomenon, anesthesia was discontinued. Cardiac arrest was induced by potassium injection in the 2 NHBD groups. Open-chest ventilation of animals was continued in all groups for 2 hours until lung explantation (Fig 1).

Donor Lung Procurement

Organ retrieval was initiated 2 hours after brain/cardiac death. Ligation of the caval veins and clamping of the

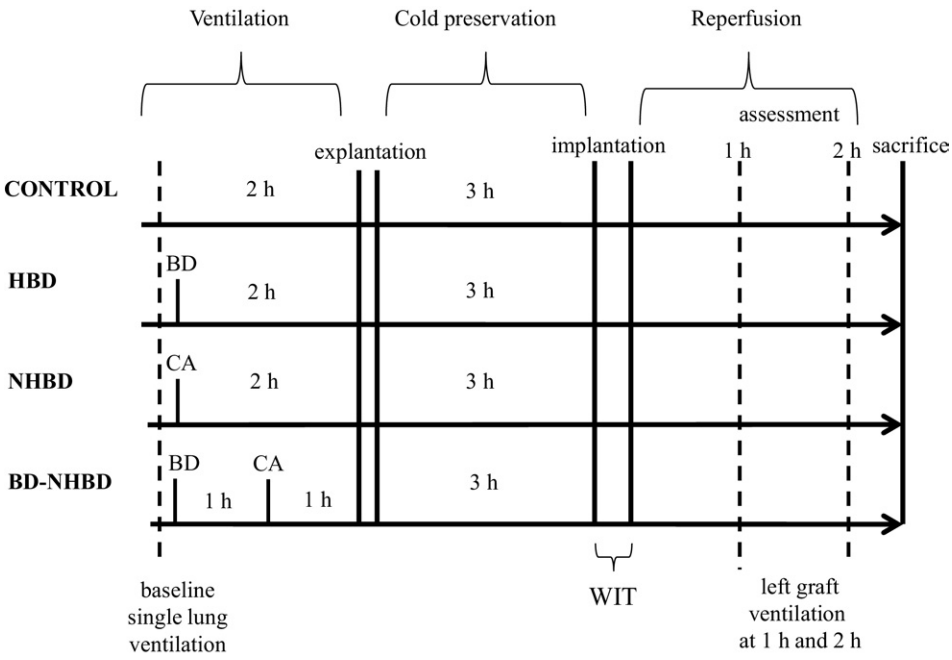

Fig 1. Experimental protocol in all groups. (BD = brain death; CA = cardiac arrest; HBD = heart-beating donor; NHBD = non–heart-beating donor; WIT = warm ischemic time.)