Deterioration of Lung Function in a Pig Model of Uncontrolled Cardiac Death

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ABSTRACT

Introduction. Uncontrolled donors after circulatory determination of death (uDCDD) represent a yet unexplored pool of organs potentially available for transplantation. The aims of this study were to validate a protocol of cardiac death in the pig and to investigate lung function during the process.

Materials and Methods. Cardiac death was induced in preanesthetized animals with an injection of 600 mg propofol; once systolic blood pressure was <50 mm Hg (Agonal Phase), a 20 mEq bolus of KCl was given and, after asystolia was documented, cardiopulmonary resuscitation (CPR) started, followed by 5 minutes no touch (end-CPR). Invasive blood pressure (BP) and heart rate (HR) were recorded; blood samples taken at baseline, 15 minutes after CPR, and after the no touch period (end-CPR). Computed tomography (CT) scans were taken at baseline and at end-CPR.

Results. Agonal phase was reached in 6 ± 1 minutes and lasted 3 ± 1 minutes; average HR was 49 ± 16 beats/min, and BP was 41 ± 12 mm Hg. CPR lasted 35 ± 3 minutes; average HR and BP were 113 ± 32 beats/min and 86 ± 63 mm Hg, respectively. PaO_2/FiO_2 decreased from 442 ± 31 mm Hg at baseline to 63 ± 36 at end-CPR ($P < .001$). pH decreased from 7.378 ± 0.045 to 6.931 ± 0.042 ($P < .001$), with a corresponding increase of lactate from 0.9 ± 0.2 to mmol/L to 12.8 ± 2.1 ($P < .001$). As assessed using CT scan, total lung volume decreased (baseline vs end-CPR 1107 ± 106 mL vs 617 ± 95; $P < .001$), whereas noninflated tissue (ie, atelectasis) significantly increased (46 ± 10 g vs 131 ± 89; $P = .008$).

Conclusions. Lung function greatly deteriorated after cardiac death. The model we set may constitute a reproducible platform for future investigations on lung uDCDD.

LUNG procurement from donors after cardio-circulatory determination of death (DCDD) could represent an important additional pool of organs to balance the gap between the number of subjects on the waiting list and the number of transplantations performed, particularly if uncontrolled donors might be taken into the picture (uDCDD). However, the complexity of events leading to uDCDD has, to date, limited procurement from these donors. Moreover, there is not much information available on lung function deterioration during sudden cardiac death. To implement preclinical models could help promote this kind of donation. The aims of this study were to validate a protocol of cardiac death in the pig and to investigate lung function during the process.

MATERIALS AND METHODS

This experimental study was performed after approval by the Ethics Committee of the Fondazione IRCCS Ca'Granda - Ospedale Maggiore Policlinico and the Italian Ministry of Health. Experiments were performed in conformity with the revised Institute of

This study was funded by Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico.

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0041-1345/16
http://dx.doi.org/10.1016/j.transproceed.2015.12.046

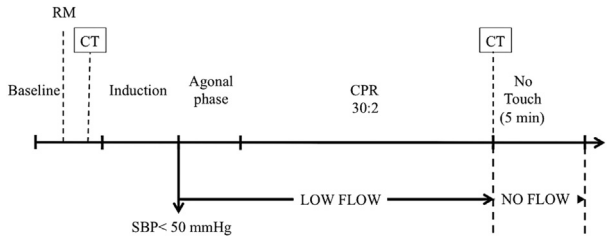

Fig. 1. Timeline. Abbreviations: RM, recruitment maneuver; CPR, cardiopulmonary resuscitation; CT, computed tomography.

Laboratory Animal Resources, Commission on Life Sciences, National Research Council Guide for the Care and Use of Laboratory Animals (National Academy Press, Washington, D.C., 1996; http://www.nap.edu/catalog/5140.html).

Anesthesia and Monitoring

Preanesthetic medication of the animals was made with an intramuscular injection of olanzapine and tiletamine 2 mg (Zoletil, VIRBAC s.r.l., Milan, Italy) and medetomidine 1 mg (Domitor, Pfizer Animal Health, Exton, Pa, United States). A continuous intravenous infusion of propofol (Diprivan, AstraZeneca, Basiglio, Milan, Italy) 10–15 mg/kg/h, medetomidine 3–6 μg/kg/h, and a bolus of contramal, 100 mg, diluted in 500 mL of 5% glucose solution were administered in the marginal auricular vein. Four-lead EKG (electrocardiogram), rectal temperature probe, and pulse oximeter were then positioned.

Under local anesthesia (200 mg of lidocaine) a tracheostomic cannula was positioned. After a bolus of 10 mg of Pancuronium Bromide, a continuous intravenous infusion of 0.4 mg/kg/h was started, and mechanical ventilation started (100% FiO_2, Vt = 8 mL/kg; respiratory rate = 16–18/min based on end-tidal CO_2; positive end expiratory pressure = 5 cmH_2O; inspiration to expiration ratio = 1:2). Intravascular catheters were positioned and secured in place in the carotid artery and jugular vein to measure arterial and central venous pressure, respectively.

Cardiac Death

A timeline of the experimental design is illustrated in Fig 1. The induction of cardiac death was started with a bolus of 600 mg of propofol. Once SBP decreased to <50 mm Hg (defined as Agonal Phase), a bolus of 20 mEq of KCl was administered to induce asystolia. Cardiopulmonary resuscitation (CPR) was started thereafter and continued for 30 minutes, alternating 30 external cardiac compressions to 2 ventilations with AMBU balloon with reservoir and high oxygen flux (12 L/min). At the end of the CPR period (end-CPR), 5 minutes of no touch period, with absence of any kind of ventilation, was performed. Hemodynamic monitoring was continuously recorded while blood was withdrawn from arterial line at baseline, at 15 minutes of CPR, and at end-CPR. Analysis of partial pressure of oxygen (pO_2), partial pressure of CO2 (pCO_2), pH, and derived variables (base excess, HCO_3^-), together with electrolytes (Na^+, K^+, Ca^{2+}, Cl^-) and lactate concentrations was performed (Radiometer ABL 800 Flex, Radiometer Medical ApS, Brønshøj, Denmark).

Computed Tomography Scan Analysis

Computed tomography (CT) scans were performed at baseline and at end-CPR, and quantitative analysis was performed as previously described [1]. Briefly, the lung profile was manually countered excluding proximal airways, lymph nodes, mediastinum, muscles, and bones (Maluna 3.15, University Hospital of Goettingen, Goettingen, Germany). Voxel density was expressed in Hounsfield units (HU), with values ranging from −1000 to 0 and +1000 HU assigned respectively to air, lung tissue, and bone. Voxel volume was 1.8 mm. We focused our attention on lung volumes as percentage of non- (HU>−100), poorly- (−100>HU>−500), well- (−500>HU>−900), and over-inflated (HU<−900) lung volume.

Statistical Analysis

All results are presented as mean ± SD. Variables were analyzed by paired *t* test or ANOVA-RM followed by Bonferroni test for all pairwise multiple comparisons. $P < .05$ was accepted as significant. Data were analyzed using Sigma Plot version 11.0 (Systat Software, Inc., GmbH, Erkrath, Germany).

RESULTS

Five domestic pigs (*Sus scrofa domesticus*) were included in the study (body weight, 24.4 ± 1.1 kg). Before induction of death (baseline), functional parameters were within normal limits: heart rate (HR) 112 ± 47; systolic blood pressure (SBP) 142 ± 47; pH 7.378 ± 0.045; and PaO_2/FiO_2 442 ± 31 mm Hg. The agonal phase was started 6 ± 5 minutes after propofol injection (SBP of 41 ± 12 mm Hg and HR of 49 ± 16 beats/min) and lasted for a total of 3 ± 1 minute before asystole was evident. CPR was carried out for a total of 35 ± 3 minutes during which, on average, SBP and HR were 86 ± 63 mm Hg and 113 ± 32 beats/min, respectively. Changes in respiratory and metabolic parameters during CPR are shown in Table 1. As shown in Fig 2, CT scan analysis showed a significant decrease of lung volume after

Table 1. Respiratory and Metabolic Variables Measured at Baseline and During CPR

	Baseline	15 min CPR	End-CPR	*P*
pH	7.378 ± 0.045	7.126 ± 0.068*	6.931 ± 0.042*,†	<.001
pCO_2 *mm Hg*	56 ± 3	69 ± 15	90 ± 21*	.013
PaO_2/FiO_2 *mm Hg*	442 ± 31	83 ± 51*	63 ± 36*	<.001
SaO_2 %	100 ± 0	76 ± 19	54 ± 29	.126
Lactate *mmol/L*	0.92 ± 0.2	8.6 ± 1.9*	12.75 ± 2.13*,†	<.001
Base Excess *mmol/L*	6.98 ± 2.54	−6.68 ± 3.51*	−12.75 ± 4.33*,†	<.001
HCO_3^- *mEq/L*	32.18 ± 2.19	21.18 ± 3.73*	17.53 ± 5.5*,†	<.001
Hb *g/dL*	8.1 ± 1.3	9.7 ± 1.5*	9.6 ± 1.6*	.015

*$P < .05$ vs baseline.
†$P < .05$ vs 15 min CPR.