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Experimental paper

Total liquid ventilation offers ultra-fast and whole-body cooling in large animals in physiological conditions and during cardiac arrest☆

Alice Hutin[a,b,c,d], Fanny Lidouren[a,b,c], Matthias Kohlhauer[a,b,c], Luc Lotteau[e], Aurélien Seemann[a,b,c], Nicolas Mongardon[a,b,c], Bertrand Renaud[d], Daniel Isabey[b,f], Pierre Carli[g], Benoit Vivien[g], Jean-Damien Ricard[h,i], Thierry Hauet[j], Richard E. Kerber[k], Alain Berdeaux[a,b,c], Bijan Ghaleb[a,b,c], Renaud Tissier[a,b,c,*]

[a] *Inserm, U955, Equipe 03, F-94000 Créteil, France*
[b] *Université Paris Est, UMR_S955, DHU A-TVB, UPEC, F-94000 Créteil, France*
[c] *Université Paris Est, Ecole Nationale Vétérinaire d'Alfort, F-94700 Maisons-Alfort, France*
[d] *Hôpitaux Universitaires Paris Centre, Cochin Hôtel-Dieu, Université Paris Descartes – Paris V , F-75014 Paris France*
[e] *Bertin Technologies, Montigny le Bretonneux F-78180, France*
[f] *Inserm, U955, Equipe 13, F-94000 Créteil, France*
[g] *SAMU de Paris, Département d'Anesthésie Réanimation, Hôpital Universitaire Necker-Enfants Malades, Université Paris Descartes – Paris V, F-75015 Paris, France*
[h] *Inserm, IAME, 1137, Univ Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France*
[i] *Assistance Publique – Hôpitaux de Paris, Hôpital Louis Mourier, Service de Réanimation Médico-chirurgicale, F-92700 Colombes, France*
[j] *Inserm, U1082, Poitiers F-86021, France*
[k] *Department of Internal Medicine, Division of Cardiovascular Medicine, University of Iowa Hospitals and Clinics, Iowa City, IA 52242, USA*

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ABSTRACT

Introduction: Total liquid ventilation (TLV) can cool down the entire body within 10–15 min in small animals. Our goal was to determine whether it could also induce ultra-fast and whole-body cooling in large animals using a specifically dedicated liquid ventilator. Cooling efficiency was evaluated under physiological conditions (beating-heart) and during cardiac arrest with automated chest compressions (CC, intra-arrest).

Methods: In a first set of experiments, beating-heart pigs were randomly submitted to conventional mechanical ventilation or hypothermic TLV with perfluoro-N-octane (between 15 and 32 °C). In a second set of experiments, pigs were submitted to ventricular fibrillation and CC. One group underwent continuous CC with asynchronous conventional ventilation (Control group). The other group was switched to TLV while pursuing CC for the investigation of cooling capacities and potential effects on cardiac massage efficiency.

Results: Under physiological conditions, TLV significantly decreased the entire body temperatures below 34 °C within only 10 min. As examples, cooling rates averaged 0.54 and 0.94 °C/min in rectum and esophageous, respectively. During cardiac arrest, TLV did not alter CC efficiency and cooled the entire body below 34 °C within 20 min, the low-flow period slowing cooling during CC.

Conclusion: Using a specifically designed liquid ventilator, TLV induced a very rapid cooling of the entire body in large animals. This was confirmed in both physiological conditions and during cardiac arrest with CC. TLV could be relevant for ultra-rapid cooling independently of body weight.

1. Introduction

For the past decade, therapeutic hypothermia (TH) has been recommended to improve survival and neurological outcome after cardiac arrest.[1] This was recently challenged by large scale clinical studies providing apparently conflicting results.[2,3] Indeed, Nielsen et al. showed that temperature management at 36 °C led to

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* Corresponding author at: Inserm, Unité 955, Equipe 3, Université Paris Est, Ecole Nationale Vétérinaire d'Alfort, 7 avenue du Général de Gaulle, 94704 Maisons-Alfort cedex, France.
E-mail address: rtissier@vet-alfort.fr (R. Tissier).

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similar benefits as conventional TH at 33 °C. Kim et al. also failed to demonstrate enhanced benefits of early instigation of TH (3), despite strong proofs of concept in animal studies.[4,5] However, conventional cooling with current techniques typically requires several hours to obtain a body temperature below 34 °C in patients (3). This is at variance with experimental studies in which animals can be cooled very rapidly, e.g., within a few minutes in mice using external cooling.[6] Is it possible to cool the human body with the same rapidity?

In this context, several techniques are currently evaluated.[7–9] For example, nasal evaporative cooling enables rapid regional head cooling in pigs (<5-min) but it requires more than 60 min to obtain whole body cooling.[7] In fact, the lung may be a better heat exchanger through a great exchange area and blood flow. It can be used with different approaches such as lung lavage with cold perfluorocarbons (PFC)[8] or inhalation of cold PFC aerosols.[9] Nevertheless, the ideal pulmonary cooling strategy is theoretically total liquid ventilation (TLV) which maximizes alveolar recruitment and PFC flow. In rabbits, TLV can cool the entire body to 32 °C within less than 15 min, while maintaining normal gas exchanges.[5,10] This improves survival and neurological outcome when induced after shockable cardiac arrest and/or myocardial infarction.[5,10] In large animals, TLV can also cool the chest very rapidly but it was poorly tolerated when induced with a non-dedicated ventilator and an industrial PFC.[11,12] In these studies, cooling efficiency was not investigated for the entire body as cold TLV was performed specifically for intra-arrest heart cooling.

In this study, our goal was to determine whether cold TLV could actually induce ultra-fast cooling of the entire body using a specifically dedicated liquid PFC ventilator for large animals. In order to mimic two different clinical scenarios, we studied the cooling capacity of hypothermic TLV in beating heart pigs but also for intra-arrest cooling during ventricular fibrillation with prolonged chest compression (CC). Importantly, TLV was instituted with perfluoro-N-octane, which was shown to be well tolerated in pigs as compared to other PFC which produced side effects in these species.[13]

2. Methods

2.1. Animal preparation

The protocol was approved by the local ethical committee (ComEth Anses/EnvA/UPEC no 16). Female pigs crossed between Large White and Landrace (20–30 kg) were anaesthetized using ketamine (20 mg/kg i.m.), acepromazine (0.25 mg/kg i.m.) and pentobarbital (10 mg/kg i.v). Animals were intubated and submitted to conventional ventilation (FiO_2 = 0.3, tidal volume = 10 ml/kg, respiratory rate = 15–18 cycles/min). Catheters were inserted into the left carotid artery and right atrium. After stabilization, hemodynamic data were continuously recorded.

2.2. Experimental protocol

In the first set of experiments, pigs were randomly submitted to hypothermic TLV or continuation of conventional ventilation (Control group). The design of the liquid ventilator is illustrated in Fig. 1A and described in Supplemental Method. It was initially

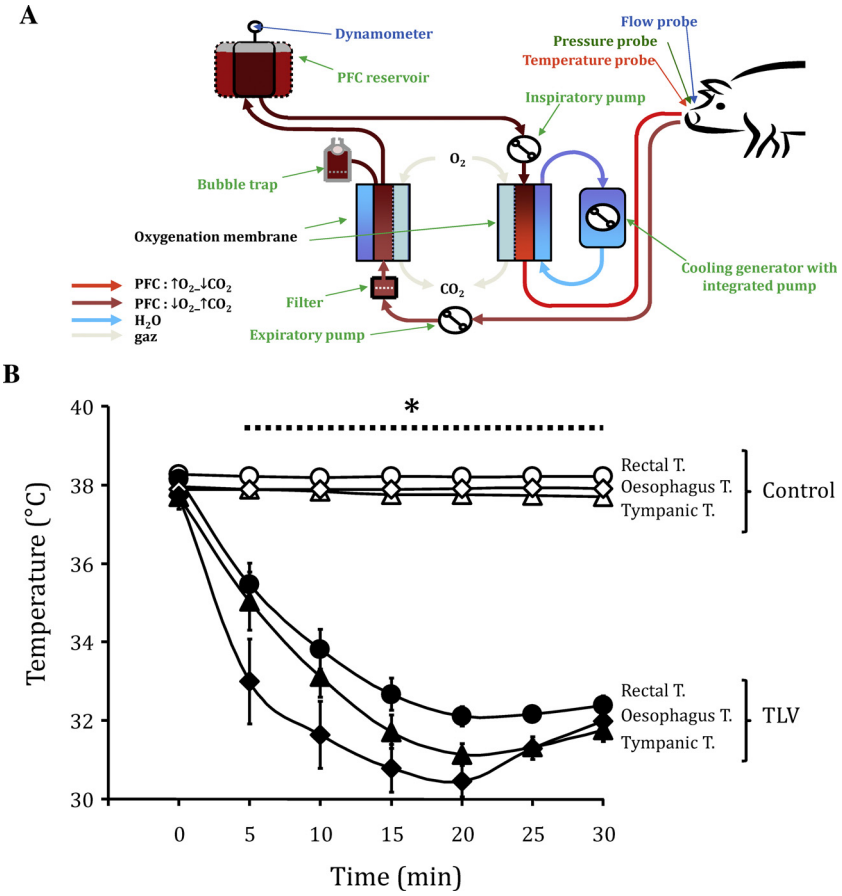

Fig. 1. Schematic representation of the liquid ventilator (Panel A) and body temperatures (Panel B) during conventional ventilation (Control group) or total liquid ventilation (TLV group) under physiological conditions (beating heart pigs). TLV, total liquid ventilation; T, Temperature; TLV, total liquid ventilation; *$p < 0.05$ for all temperatures between TLV and Control groups.