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Control of rapid hypothermia induction by total liquid ventilation : Preliminary results

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Abstract— **Mild therapeutic hypothermia (MTH) consists in cooling the body temperature of a patient to between 32 and 34 °C. This technique helps to preserve tissues and neurological functions in multi-organ failure by preventing ischemic injury. Total liquid ventilation (TLV) ensures gas exchange in the lungs with a liquid, typically perfluorocarbon (PFC). A liquid ventilator is responsible for ensuring cyclic renewal of tidal volume of oxygenated and temperature-controlled PFC. Hence, TLV using the lung as a heat exchanger and PFC as a heat carrier allows ultra fast cooling of the whole body which can help improve outcome after ischemic injuries. The present study was aimed to evaluate the control performance and safety of automated ultra-rapid MTH induction by TLV. Experimentation was conducted using the Inolivent-5.0 liquid ventilator equipped with a PFC treatment unit that allows PFC cooling and heating from the flow of energy carrier water inside a double wall installed on an oxygenator. A water circulating bath is used to manage water temperature. A feedback controller was developed to modulate inspired PFC temperature and control body temperature. Such a controller is important since, with MTH induction, heart temperature should not reach 28 °C because of a high risk of fibrillation. The *in vivo* experimental protocol was conducted on a male newborn lamb of 4.7 kg which, after anesthetization, was submitted to conventional gas ventilation and instrumented with temperature sensors at the femoral artery, oesophagus, right ear drum and rectum. After stabilization, TLV was initiated with fast automated MTH induction to 33.5 °C until stabilization of all temperatures. MTH could be reached safely in 3 minutes at the femoral artery, in 3.6 minutes at the esophagus, in 7.7 minutes at the eardrum and in 15 minutes at the rectum. All temperatures were stable at 33.5 ± 0.5 °C within 15 minutes. The present results reveal that ultra-fast MTH induction by TLV with Inolivent-5.0 is safe for the heart while maintaining esophageal and arterial temperature over 32.6 °C.**

I. INTRODUCTION

Mild therapeutic hypothermia (MTH) consists in cooling body temperature to between 32 °C and 34 °C [1]. MTH is known to improve outcome in many clinical scenarios [2]. Some studies have shown that early and rapid induction of hypothermia can limit the number of cells from entering apoptosis or necrosis [3]. In clinical applications, most hypothermia induction methods use surface cooling with MTH achieved in hours [4]. Some less conventional cooling methods such as intra-nasal devices, intra-vascular catheters and water bath immersion can reach MTH within an hour [5] [6] [7]. Another less common method is extracorporeal circulation which can reach cooling rates as fast as -25 °C/h [8].

Total liquid ventilation (TLV) is an emerging and promising mechanical ventilation method in which the lungs are completely filled with liquid, typically perfluorocarbon (PFC). A dedicated liquid ventilator ensures gas exchange by renewal of a tidal volume (Vt) of liquid that is filtered, controlled to desired temperature, oxygenated and free of CO_2 [9]. It offers many advantages over conventional mechanical ventilation, such as the use of lower inflation pressure by increasing lung compliance [10], homogeneous ventilation [11], anti-inflammatory effects [12] and can also induce efficient lung lavage [13]. TLV can also be applied outside of exclusive respiratory support and has shown promise for ultra-fast MTH induction [14].

Indeed, MTH induction by liquid ventilation with cold PFC has shown good potential with a cooling rate at least as rapid as extracorporeal circulation. Some published studies have reached whole body MTH induction by TLV within 20 minutes for rabbits [15] while other studies have reported reaching MTH in approximately 30 minutes for cats [16] and newborn lambs [17]. Although, published studies involving liquid ventilation-induced hypothermia have reported the use of different PFC types with PFC temperatures ranging from 4 to 30 °C and minute ventilation (V_{min}) varying from 17 to 68 ml/min/kg, none have used a body temperature control algorithm [18] [17] [16].

MTH is the only type of hypothermia used for whole-body therapeutic purposes since the heart spontaneously fibrillates in most mammals below 28 °C [19]. Using lungs as a heat exchanger to induce MTH can be very effective in liquid ventilation but causes the heart to cool very rapidly before most other organs [20]. Hence, while ultra-fast MTH induction by TLV is a promising technique, the problem remains the absence of a device for automatic and safe body temperature control.

Our multidisciplinary Sherbrooke research team has focused on the advancement of total liquid ventilation by developing a safe and efficient liquid ventilator for preclinical studies [21] [22]. The present study aimed to evaluate both the performance and safety of an automated ultra-fast body cooling device integrated to our liquid ventilator prototype,

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Fig. 1: Liquid ventilator prototype Inolivent-5.0

Inolivent-5.0 (figure 1).

II. MATERIALS AND METHOD

A. Body temperature control by a liquid ventilator

The Inolivent-5.0 liquid ventilator uses two independent piston pumps to insert and withdraw PFC liquid in the lungs, with four pinch valves synchronized to guide the PFC flow in the ventilator (figure 2). A Y-connector is used to connect both liquid and conventional ventilator to the patient. A 0.2 micron filter receives the expired PFC before it returns in the integrated PFC treatment unit for hypothermia (PTUh). The PTUh contains a gas exchanger to control F_iO_2, a condenser to retrieve PFC vapor, a two-column oxygenator for PFC oxygenation and CO_2 removal, and a buffer reservoir (figure 3). Total PFC volume inside the liquid ventilator is 3 liters. Each column of the PTUh has a double wall: the exterior wall consisting of polycarbonate and the inner cylinder made of stainless steel (thickness 0.8 mm). The water flowing between the walls is used as a heat carrier for modulating the temperature of the PFC inside the PTUh (figure 3). A 6-liter water circulating bath (Model 9100, PolyScience, It) is used to heat or cool the temperature of the circulating water. Control of body temperature is achieved by varying the inspired PFC temperature through modulation of the water temperature. The user specifies the targeted body temperature via the user interface of Inolivent-5.0 upon which the feedback controller automatically modulates the bath temperature set point to achieve this desired body temperature.

B. In-vivo validation protocol

The experimental protocol was approved by our institutional Ethics Committee for Animal Care and Experimentation. For these preliminary results, one healthy 4-day old male lamb weighing 4.7 kg was orally intubated with a 4.5 mm cuffed endotracheal tube and restrained in supine position. The newborn lamb was then anaesthetized with propofol and ventilated with a conventional mechanical ventilator (Siemens Servo 300 ventilator, Solna, Sweden) in a pressure regulated, volume controlled (PRVC) mode

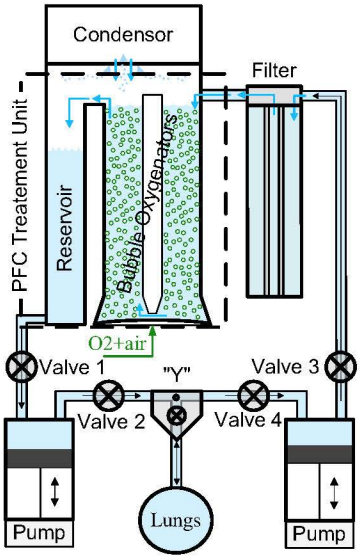

Fig. 2: PFC circuit in liquid ventilator Inolivent-5.0

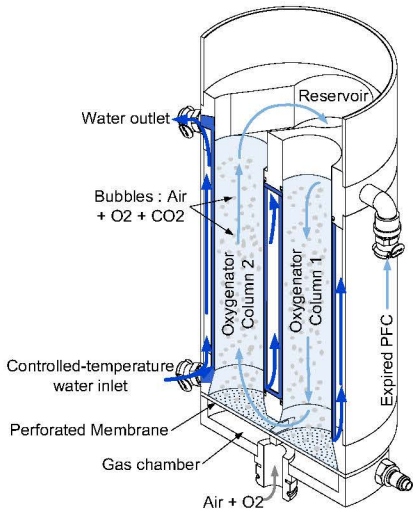

Fig. 3: PFC treatment unit (PTUh) for hypothermia induction

with positive end expiratory pressure ($PEEP_{ref}$) of 4 cmH_2O, Vt = 10 ml/kg and respiratory frequency (Fr) of 55 breaths/minute. A 4 Fr femoral arterial catheter (PiCCO, Pulsion Medical, Munich, Germany) was installed for arterial blood gas analysis sampling and temperature recording. In addition, temperature sensors were inserted in the esophagus at the atrial level, in the right ear next to the eardrum and in the rectum at a depth of 5 cm.

After a 30 min recovery period, the lamb was paralyzed with rocuronium bromide and shifted from conventional mechanical ventilation (CMV) to a pressure-controlled pressure-limited total liquid ventilation using the Inolivent-5.0 prototype and the body temperature controller. Transition was carried out as quickly as possible using one 25 ml/kg aliquot of 20 °C preoxygenated PFC (Perfluorobron, Exfluor, Round Rock, USA). Hypothermic TLV was performed at the

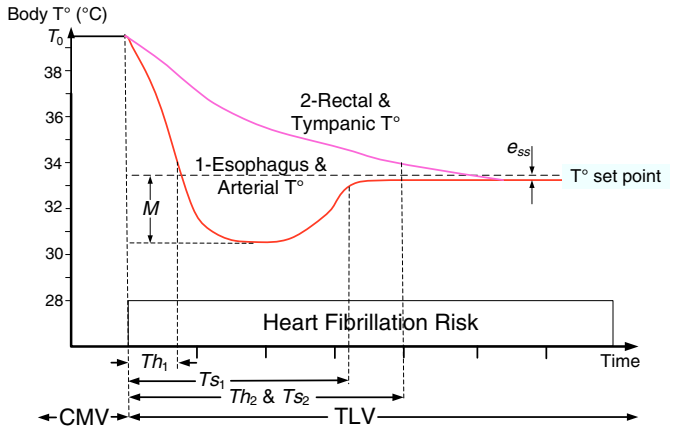

Fig. 4: Typical body temperature curves, initial temperature (T_0), settling time (T_s), time to 34 °C (T_h) and overshoot (M) while automated MTH induction by TLV

following initial ventilator settings: $PEEP_{ref}$ = 1 cmH_2O, Fr = 6.4 breaths/min and Vt = 15 ml/kg. Inspiration was volume-regulated while expiration was pressure-regulated; both were volume-controlled, pressure-limited and time-cycled. Throughout the first cycles of TLV, Vt was raised to 20 ml/kg.

TLV began with fast MTH induction to 33.5 °C until stabilization of all temperatures. Figure 4 shows typical body temperature curves and measured parameters. Heart temperature is estimated to approximate that of arterial and esophageal temperatures. At the outset, esophageal and arterial temperatures decreased rapidly, compared to rectal and tympanic temperatures. Overshoot of temperatures is noted (M), settling time at 33.5 ± 0.5 °C (T_s), steady state error (e_{ss}) and time to reach MTH (T_h), and depicted in figure 4.

Control performances targeted are that M should be greater than -5.5 °C, such that temperature does not reach 28 °C at any time, while all T_h and T_s times should be less than 20 min and e_{ss} in the range of ± 0.5 °C.

III. RESULTS

Figure 5 a and b depict liquid ventilator temperatures ans body temperatures respectively. The temperature control began after 2 min only, in order to allow PFC homogenization in the lungs and air evacuation. In the first phase, water is heated rapidly and the bath temperature set point becomes saturated at 40 °C because of the rapid fall in body temperature. At this time, inspired PFC is heated to around 30.5 °C. During the second phase, water temperature is decreased rapidly by the controller in order to stabilize both inspired PFC temperature and body temperatures. In the last phase, water and PFC temperatures converge simultaneously with body temperatures.

Table I summarizes T_O, T_h, T_s, M and e_{ss} values. During the first phase, arterial and esophageal temperatures rapidly fall to reach T_h after respectively 3 and 3.5 minutes (figure 5 b). These drops in temperature are slowed by inspired PFC

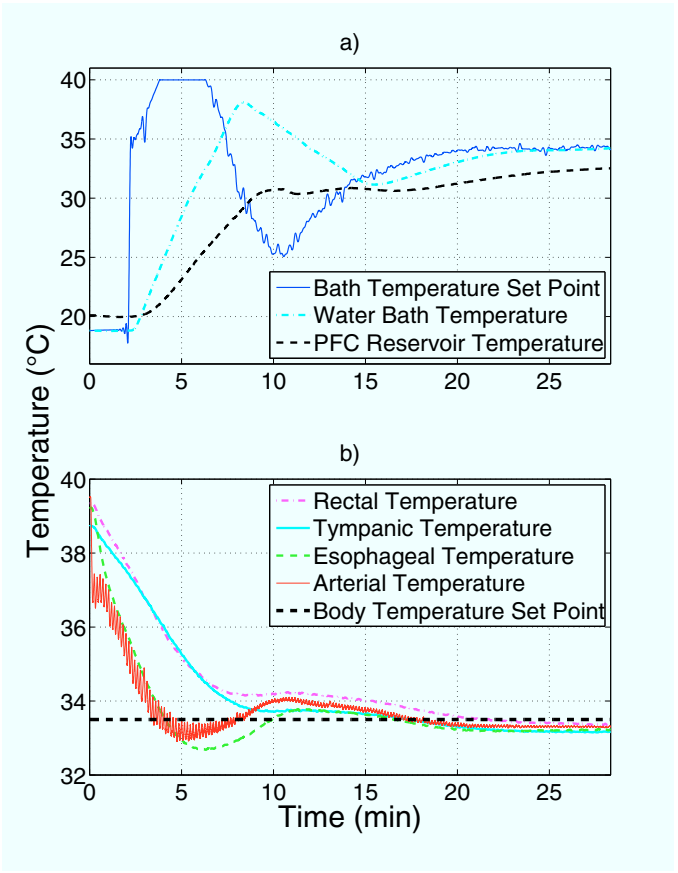

Fig. 5: a) Liquid ventilator temperatures during automatized ultra-fast hypothermia induction by TLV. b) Body temperatures while ultra-fast mild therapeutic hypothermia induction by TLV

being heated, although there are still overshoots of respectively -0.6°C and -0.9°C, respectively. Oscillations of ∼0.3 °C in arterial temperature are in phase with expiration and inspiration cycles. Throughout the second phase, esophageal and arterial temperatures are heated by the rest of body while inspired PFC remains at approximately 30.5 °C. Tympanic and rectal temperatures reach T_h and T_s after respectively 7.7 minutes and 15 minutes. After 25 minutes, all temperatures have now converged with steady state errors ranging from -0.2 to -0.3 °C depending on measurement sites.

IV. DISCUSSION

PFC temperature is initiated at 20 °C in order to use PFC inertia to achieve a steep downward slope at beginning of TLV. MTH induction by TLV thus exhibits cooling rates faster than all conventional hypothermia induction method and similar to extracorporeal circulation.

While negative overshoots were observed on arterial and esophageal temperatures during MTH induction by TLV on the newborn lamb, these overshoots should not cause any serious risks of cardiac arrhythmia since temperatures remained over °C. It would even be possible to allow these temperatures to go lower and maintain them to decrease

TABLE I: Initial temperatures (T_0), time for body temperature to reach mild hypothermia (T_h), settling time (T_s), temperature overshoots (M) and steady state errors (e_{ss}) while automated hypothermia induction by TLV with Inolivent-5.0

Sensor	T_0 °C	T_h min	T_s min	M °C	e_{ss} °C
Artery	39.5	3.0	12.1	-0.6	-0.2
Esophagus	39.2	3.6	8.2	-0.9	-0.2
Ear drum	38.7	7.7	7.7	None	-0.3
Rectum	39.4	15.0	15.0	None	-0.2

T_h and T_s at the eardrum and rectum. Preliminary results revealed that T_s can be reached safely in 15 minutes on all measurement sites with a maximal error of 0.3 °C with the target.

V. CONCLUSION

The liquid ventilator Inolivent-5.0 can induce automated ultra-fast body cooling to 33.5 °C by TLV. Preliminary results on a newborn lamb reveal that MTH can be achieved safely in 15 minutes for the whole body without cardiac risk while providing acceptable steady body temperatures. Future investigation will consist in conducting the study on a larger group of newborn lambs as well as test the Inolivent-5.0 MTH induction feedback controller on a rabbit model.

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REFERENCES

[1] H. after Cardiac Arrest Study Group, "Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest." *N Engl J Med*, vol. 346, no. 8, pp. 549–556, Feb 2002.

[2] J. Varon and P. Acosta, "Therapeutic hypothermia: past, present, and future." *Chest*, vol. 133, no. 5, pp. 1267–1274, May 2008. [Online]. Available: http://dx.doi.org/10.1378/chest.07-2190

[3] K. H. Polderman, "Application of therapeutic hypothermia in the icu: opportunities and pitfalls of a promising treatment modality. part 1: Indications and evidence." *Intensive Care Med*, vol. 30, no. 4, pp. 556–575, Apr 2004. [Online]. Available: http://dx.doi.org/10.1007/s00134-003-2152-x

[4] K. Polderman, "Application of therapeutic hypothermia in the intensive care unit. opportunities and pitfalls of a promising treatment modality–part 2: Practical aspects and side effects." *Intensive Care Med*, vol. 30, no. 5, pp. 757–769, May 2004. [Online]. Available: http://dx.doi.org/10.1007/s00134-003-2151-y

[5] M. R. Wolfson, D. J. Malone, J. Wu, J. Hoffman, A. Rozenberg, T. H. Shaffer, and D. Barbut, "Intranasal perfluorochemical spray for preferential brain cooling in sheep." *Neurocrit Care*, vol. 8, no. 3, pp. 437–447, 2008. [Online]. Available: http://dx.doi.org/10.1007/s12028-008-9064-0

[6] M. W. Dae, D. W. Gao, D. I. Sessler, K. Chair, and C. A. Stillson, "Effect of endovascular cooling on myocardial temperature, infarct size, and cardiac output in human-sized pigs." *Am J Physiol Heart Circ Physiol*, vol. 282, no. 5, pp. H1584–H1591, May 2002. [Online]. Available: http://dx.doi.org/10.1152/ajpheart.00980.2001

[7] O. Plattner, A. Kurz, D. I. Sessler, T. Ikeda, R. Christensen, D. Marder, and D. Clough, "Efficacy of intraoperative cooling methods." *Anesthesiology*, vol. 87, no. 5, pp. 1089–1095, Nov 1997.

[8] S. A. Mayer, *Therapeutic Hypothermia*, M. Dekker, Ed. Library of Congress, 2005.

[9] M. L. Costantino, P. Micheau, T. H. Shaffer, S. Tredici, M. R. Wolfson, 6th Internationl Symposium on Perfluorocarbon Application, and L. Ventilation, "Clinical design functions: round table discussions on the bioengineering of liquid ventilators." *ASAIO J*, vol. 55, no. 3, pp. 206–208, 2009.

[10] M. R. Wolfson, J. S. Greenspan, K. S. Deoras, S. D. Rubenstein, and T. H. Shaffer, "Comparison of gas and liquid ventilation: Clinical, physiological and histological correlates," *JAP*, vol. 72, no. 3, pp. 1024–1031, 1992.

[11] M. R. Wolfson and T. H. Shaffer, "Pulmonary applications of perfluorochemical liquids: Ventilation and beyond," *Paediatric Respiratory Reviews*, vol. 6, no. 2, pp. 117–127, Jun. 2005. [Online]. Available: http://www.sciencedirect.com/science/article/B6WP5-4G6YF84-8/2/4c33551471f3b314f6b1f0509d535ed2

[12] S. S. Yang, M. J. Jeng, R. McShane, C. Y. Chen, M. R. Wolfson, and T. H. Shaffer, "Cold perfluorochemical-induced hypothermia protects lung integrity in normal rabbits," *Biol.Neonate*, vol. 87, pp. 60–65, 2005.

[13] O. Avoine, D. Bosse, B. Beaudry, A. Beaulieu, R. Albadine, J.-P. Praud, R. Robert, P. Micheau, and H. Walti, "Total liquid ventilation efficacy in an ovine model of severe meconium aspiration syndrome." *Crit Care Med*, Feb 2011. [Online]. Available: http://dx.doi.org/10.1097/CCM.0b013e31820ead1a

[14] R. Tissier, K. Hamanaka, A. Kuno, J. C. Parker, M. V. Cohen, and J. M. Downey, "Total liquid ventilation provides ultra-fast cardioprotective cooling." *J Am Coll Cardiol*, vol. 49, no. 5, pp. 601–605, Feb 2007. [Online]. Available: http://dx.doi.org/10.1016/j.jacc.2006.09.041

[15] M. Chenoune, F. Lidouren, C. Adam, S. Pons, L. Darbera, P. Bruneval, B. Ghaleb, R. Zini, J.-L. Dubois-Rande, P. Carli, B. Vivien, J.-D. Ricard, A. Berdeaux, and R. Tissier, "Ultrafast and whole-body cooling with total liquid ventilation induces favorable neurological and cardiac outcomes after cardiac arrest in rabbits." *Circulation*, Aug 2011. [Online]. Available: http://dx.doi.org/10.1161/CIRCULATIONAHA.111.039388

[16] T. H. Shaffer, D. L. Forman, and M. R. Wolfson, "Physiological effects of ventilation with liquid fluorocarbon at controlled temperatures." *Undersea Biomed Res*, vol. 11, no. 3, pp. 287–298, Sep 1984.

[17] D. L. Forman, V. K. Bhutani, N. Tran, and T. H. Shaffer, "A new approach to induced hypothermia." *J Surg Res*, vol. 40, no. 1, pp. 36–42, Jan 1986.

[18] S. B. Harris, M. G. Darwin, S. R. Russell, J. M. O'Farrell, M. Fletcher, and B. Wowk, "Rapid (0.5 degrees c/min) minimally invasive induction of hypothermia using cold perfluorochemical lung lavage in dogs." *Resuscitation*, vol. 50, no. 2, pp. 189–204, Aug 2001.

[19] R. Tissier, M. Chenoune, B. Ghaleb, M. V. Cohen, J. M. Downey, and A. Berdeaux, "The small chill: mild hypothermia for cardioprotection?" *Cardiovasc Res*, vol. 88, no. 3, pp. 406–414, Dec 2010. [Online]. Available: http://dx.doi.org/10.1093/cvr/cvq227

[20] M. Chenoune, F. Lidouren, B. Ghaleb, N. Couvreur, J.-L. Dubois-Rande, A. Berdeaux, and R. Tissier, "Rapid cooling of the heart with total liquid ventilation prevents transmural myocardial infarction following prolonged ischemia in rabbits." *Resuscitation*, vol. 81, no. 3, pp. 359–362, Mar 2010. [Online]. Available: http://dx.doi.org/10.1016/j.resuscitation.2009.12.005

[21] P. Micheau, R. Robert, B. Beaudry, A. Beaulieu, M. Nadeau, O. Avoine, M. E. Rochon, J.-P. Praud, and H. Walti, *Progress in Molecular and Environmental Bioengineering - From Analysis and Modeling to Technology Applications*. Intech, 2011, ch. A Liquid Ventilator Prototype for Total Liquid Ventilation Preclinical Studies, p. 646.

[22] R. Robert, P. Micheau, O. Avione, B. Beaudry, A. Beaulieu, and H. Walti, "A regulator for pressure controlled total liquid ventilation," *IEEE Transactions on Biomedical Engineering*, vol. 57, no. 9, pp. 2267 – 2276, 2009.