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Patient-specific optimal cooling power command for hypothermia induction by liquid ventilation

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ABSTRACT

While it is known that total liquid ventilation can rapidly cool animal subjects and improve outcomes after cardiac arrest, the temperature control strategy of the liquid ventilator for clinical use remains unknown. This work proposes to control the cooling power of the liquid ventilator in two phases. The first phase consists in a null cooling power command in order to estimate cardiac output. During the second phase, the optimal cooling power command dedicated to the estimated cardiac output is sent to the cooling system. The simulated results in human adults allow predicting the cooling performances and the overall safety.

1. Introduction

Out-of-hospital cardiac arrest is a leading cause of death worldwide and is associated with a major socioeconomic cost. The current European Resuscitation Council has issued a strong recommendation for a targeted temperature management between 32 °C and 36 °C of a patient after cardiac arrest (Nolan et al., 2015). Moreover, reducing body temperature to reach mild therapeutic hypothermia (32–34 °C) has been proposed to improve neurological recovery after resuscitation and has also been promoted as an improvement of the long-term quality of life of cardiac arrest survivors (Patel & Parikh, 2016). The neurological benefit of hypothermia has been challenged by recent trials, and more experimental findings support the premise that hypothermia should be induced much earlier. Since current cooling methods are slow (4–6 h to cool a patient Kim et al., 2014), new techniques have been investigated in order to dramatically reduce the hypothermia induction time (Forman, Bhutani, Tran, & Shaffer, 1986; Harris et al., 2001; Kohlhauer et al., 2016; Wolfson et al., 2008). One of the most appealing methods of rapid hypothermia induction is the use of a liquid ventilator to fill the lung with a temperature-controlled breathable liquid (Nadeau et al., 2015). To date, such a revolutionary ultrafast cooling method is not used in humans. However, preclinical experimentations with animal models demonstrate that ultrafast hypothermia induction with a liquid ventilator can dramatically improve survival rates as well as provide potent neuroprotection and cardioprotection after cardiac arrest (Chenoune et al., 2011). These latter results thus represent a strong motivation to develop highly efficient and safe cooling strategies using total liquid ventilation (TLV) for post-cardiac arrest in human patients.

TLV is an innovative mechanical ventilation method in which the lung is filled with a breathable perfluorocarbon (PFC) liquid (Shaffer, Wolfson, Greenspan, Rubenstein, & Stern, 1994). A dedicated liquid ventilator must be used in order to ensure gas exchange by a mechanically forced inspiration and expiration of the tidal volumes (Vt) of PFC into the lung (Robert et al., 2006). The instilled PFC must be oxygenated and the CO_2 must be removed (Micheau et al., 2011). The breathable liquid must also be temperature-controlled enabling to efficiently manage the patient's body temperature (Nadeau et al., 2014).

When the lung is filled with a breathable liquid, it turns into a massive heat capacity and a powerful heat exchanger with the pulmonary circulation (Forman et al., 1986), without altering hemodynamics or respiratory mechanics (Sage et al., 2016). According to studies using hypothermic TLV, the use of PFC in the airways is safe and beneficial with PFC temperature as low as 4 °C (Harris et al., 2001; Yang et al., 2005). The safety challenge is to avoid a decrease in arterial temperature below 31.5 °C during the cooling process in order to protect the subject from cardiac arrhythmia due to a too-low heart temperature (Polderman & Herold, 2009).

In previous studies, we described how the thermal dynamics in total liquid ventilation can be modeled with a fully parameterized lumped thermal mathematical model (Nadeau et al., 2015, 2017). This model

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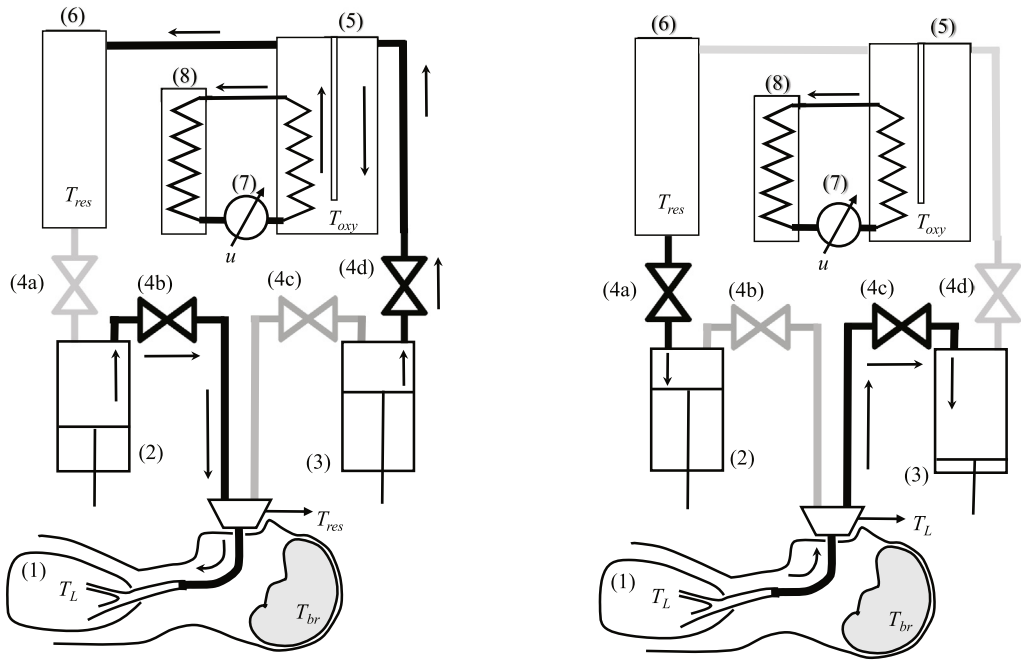

Fig. 1. Schematic representation of the Inolivent liquid ventilator prototype connected to a patient: inspiration phase with inspired liquid at the temperature T_{res} (left), expiration phase with expired liquid at the temperature T_L (right). Gray circuits are without liquid flow. Black circuits are with liquid flow.

was validated in newborn lambs, juvenile lambs and an adult sheep undergoing rapid hypothermia induction by total liquid ventilation. It was hypothesized that the translation of our mathematical model for humans can be acceptable (Nadeau et al., 2017). As a result, we have demonstrated that it was possible to compute the optimal temperature of the instilled liquid into the lung. The computation method and the results were presented at the 20th World Congress of the International Federation of Automatic Control (IFAC) (Micheau, Nadeau, Tissier, & Walti, 2017). It also showed that one of the most sensitive parameters on cooling performances and safety of the inspired temperature control is the cardiac output (Q) (Nadeau et al., 2017). Moreover, in post-cardiac arrest patient, cardiac output can vary over a very large range $Q \in [3 \quad 8]$ L/min (Bro-Jeppesen et al., 2014). When the value of Q is unknown, it was demonstrated that the optimal command of the instilled liquid temperature defined for the worst-case scenario ($Q = 3$ L/min) can be safely used for all patients (Micheau et al., 2017).

The problem addressed in the present analysis is to consider the cooling system of the liquid ventilator. Hence, the cooling power command of the liquid ventilator is the command input instead of the instilled liquid temperature. With this input command, it is possible to propose a control strategy in two phases in order to solve the concerns raised by the uncertain cardiac output after cardiac arrest. In the first phase, the cooling power command is null, the lung temperature response is measured in order to estimate cardiac output ($\hat{Q}$). The second phase consists in applying the direct optimal control by considering a perfect estimation, $Q = \hat{Q}$. Since the cardiac output is estimated for each patient during the first phase, the cooling power command is patient-specific (Rees & Karbing, 2016).

In Section 2, the thermal models of the liquid ventilator and the patient are developed. The resulting continuous state-space time-varying model is then used to compute the optimal command of the cooling power as a function of cardiac output.

Section 3 presents the numerical simulations of the thermal model projected to a human adult with normal physiological parameters (Nadeau et al., 2017). The performances and safety of the command are evaluated when the cardiac output is similar or differs from the estimated value, $Q \neq \hat{Q}$.

2. The control strategy

2.1. The system: The liquid ventilator

The Inolivent liquid ventilator prototype is schematically shown in Fig. 1 (Micheau et al., 2011). It is dedicated to ventilate the lung completely filled with a breathable liquid (Robert et al., 2009). To date, it is only used to perform experimental research with mammals.

The ventilator is connected to the patient via the Y-connector. The four pinch valves (4a, 4b, 4c, 4d) are programmed to guide the liquid flow to the lung. During the inspiration phase, the valves (4b) and (4d) are open, and the valves (4a) and (4c) are closed. The inspiratory pump (2) inserts the PFC through the endotracheal tube to the lung. Hence, the liquid arrives directly to the lung (1) from the reservoir (6) at the controlled temperature T_{res}. Simultaneously, the expiratory pump (3) returns a tidal volume of liquid (previously expired from the lung (1)) to the oxygenator (5). During the expiration phase, the valves (4b) and (4d) are closed, and the valves (4a) and (4c) are open. The expiratory pump (3) withdraws the PFC through the endotracheal tube from the lung. Simultaneously, the inspiratory pump (2) is filled with a tidal volume of liquid pumped from the reservoir (6). The liquid temperature that directly arrives from the lung (1) is measured at the patient connector location. At the end of expiration, this temperature measurement at the Y-connector can be used to calculate an indirect measurement of the lung temperature T_L (Nadeau et al., 2014).

The function of the oxygenator (5) is to oxygenate the liquid and to control its temperature. The oxygen and carbon dioxide concentrations in the PFOB is monitored and controlled by a gas mixer (not shown) (Micheau et al., 2011). Water flowing within the double walls of the oxygenator is used for cooling the PFC inside the oxygenator before its re-instillation into the lung. The water is pumped from a cooling system (8) to the oxygenator (5) at a controlled mass flow rate with a pump (7). Hence, the command u of the pump (7) allows controlling the cooling power (P) of the thermal exchange in the oxygenator. When there is no inflow of water in the oxygenator, there is no cooling power in the latter, $u = 0$. When there is maximal inflow of water in the oxygenator, the maximal cooling power is applied to the oxygenator.