Abstract—Goal: Recent preclinical studies have shown that therapeutic hypothermia induced in less than 30 min by total liquid ventilation (TLV) strongly improves the survival rate after cardiac arrest. When the lung is ventilated with a breathable perfluorocarbon liquid, the inspired perfluorocarbon allows us to control efficiently the cooling process of the organs. While TLV can rapidly cool animals, the cooling speed in humans remains unknown. The objective is to predict the efficiency and safety of ultrafast cooling by TLV in adult humans. Methods: It is based on a previously published thermal model of ovines in TLV and the design of a direct optimal controller to compute the inspired perfluorocarbon temperature profile. The experimental results in an adult sheep are presented. The thermal model of sheep is subsequently projected to a human model to simulate the optimal hypothermia induction and its sensitivity to physiological parameter uncertainties. Results: The results in the sheep showed that the computed inspired perfluorocarbon temperature command can avoid arterial temperature undershoot. The projection to humans revealed that mild hypothermia should be ultrafast (reached in fewer than 3 min (−72 °C/h) for the brain and 20 min (−10 °C/h) for the entire body). Conclusion: The projection to human model allows concluding that therapeutic hypothermia induction by TLV can be ultrafast and safe. Significance: This study is the first to simulate ultrafast cooling by TLV in a human model and is a strong motivation to translate TLV to humans to improve the quality of life of postcardiac arrest patients.

Index Terms—Hypothermia, liquid ventilation, optimal control, targeted temperature management, thermal modeling.

I. INTRODUCTION

PATIENTS successfully resuscitated from cardiac arrest often present very severe neurological and cardiac dysfunctions within minutes following resumption of spontaneous circulation. One of the strategies able to improve their prognosis is mild therapeutic hypothermia (MTH) which consists of cooling down the body to 32–34 °C. Yet, it has been shown that timing to reach target temperature is one of the critical points for the efficacy of such strategy and any delay in cooling has deleterious consequences for the prognosis [1]. Experimental evidences even suggest that most of the benefit is lost when target temperature is reached after 30 min following resumption of spontaneous circulation [2], [3]. Currently, application of MTH in patients is performed by cold blankets and cold saline intravenous infusion which takes about 4 hours to reach target temperature [4], [5]. In this context, we here propose to investigate Total Liquid Ventilation (TLV) as a new method to provide ultrafast induction of therapeutic hypothermia.

TLV is an emerging and promising method for ultrafast cooling of body temperature in which the lung is filled with a temperature-controlled perfluorocarbon liquid (PFC) [6], [7]. The PFCs used in TLV, such as perfluoron (PFOB), are nontoxic, chemically stable, with a low surface tension and a high propensity to dissolve respiratory gases [8]. Moreover, PFOB is approved in humans for lung lavage and has been used in previous clinical studies for partial liquid ventilation [9]. Due to their high volumetric thermal capacity—over 500 times that of air—PFCs represent an efficient heat exchange medium. When the lung is filled with PFC, it turns into both a huge heat capacity and a powerful heat exchanger with the pulmonary circulation, without altering hemodynamics or respiratory mechanics [10], [11]. However, one instillation of PFC equivalent to the functional residual capacity is not sufficient to achieve MTH; it is therefore necessary to periodically renew a tidal volume of PFC into the lung. Hence, as in the case of a conventional mechanical
ventilator, a liquid ventilator can fill the lung and ensure patient ventilation with a temperature-controlled PFC [12]. Many preclinical studies have proven that MTH induction by TLV is not deleterious for the lung functions and that subject can be rapidly weaned [2], [13]–[16]. Therefore, there is a strong motivation to evaluate the efficiency of MTH induction by TLV in adult human model.

In a previous study, we described how the thermal dynamics in TLV can be modeled with a fully parameterized lumped thermal mathematical model [17]. This model was validated in a group of 6 newborn and 6 juvenile lambs (2.8 to 23.6 kg) undergoing rapid MTH induction by TLV. The results showed that rapid hypothermia induction by TLV can be divided into two phases: i) the initial filling and ventilation of the lung with an inspired PFC at low temperature (10 to 25 °C) for the first minutes and ii) the progressive increase of the inspired PFC temperature for core temperature stabilization. In some cases, the systemic arterial temperature appeared to undershoot below the targeted temperature in the first phase [17]. In other words, while the efficiency of the method was both validated experimentally and explained mathematically, it nevertheless remained problematic due to observed temperature undershoots in certain instances.

In view of the projected clinical application of ultrafast MTH induction by TLV, the objective of the present study is to predict and control both the efficiency and safety of the method. The efficiency objective for the cooling speed is to remain ultrafast (MTH reached in fewer than 30 min (less than −6 °C/h) for the whole body and fewer than 10 min (less than −18 °C/h) for the brain) when projected to large mammals (adult sheep) and finally to human adult model. The safety objective is to avoid a decrease in arterial temperature below the targeted core body temperature during the cooling process in order to avoid the risk of cardiac arrhythmia [18].

The sheep model is well documented to closely represent the human lung function as well as the physiological parameters of flow, resistance, compliance, respiratory frequency and tidal volume of humans [19], [20]. Hence, we hypothesize that the translation of our mathematical model from lambs to sheep, and finally to adult humans should be acceptable.

Section II presents the thermal mathematical model validated in lambs [17] and is presented as a continuous time-varying state-space model. Due to the periodical cycling of ventilation, it is transformed into a discrete state-space model in order to reduce the computation time. This newly developed cycle-by-cycle thermal mathematical model can be used by an optimizer under constraints to design the direct optimal controller of the inspired PFC temperature [21].

Section III presents the animal experimentation of ultrafast hypothermia induction by TLV in a 61 kg adult sheep. Experimental results are used for the fine-tuning of the thermal model and presentation of the various body temperatures. The thermal model is then used to compute a posteriori the optimal inspired PFC temperature to ensure a safe and efficient hypothermia induction.

Section IV presents the projection of the thermal model to a human adult with normal physiological parameters. The projected thermal model and the direct optimal controller are then used to compute an optimal hypothermia induction by TLV. The limitations of the method are assessed by performing a sensitivity analysis to explore the impact of parametric uncertainties in the model. Finally, using the sensitivity analysis results, a worst-case optimal control is proposed to avoid undershooting irrespective of the patient’s physiological parameters.

II. MATHEMATICAL MODEL AND CONTROL

A. Continuous Time-Varying State-Space Model

The parametric lumped thermal model of the lung and body is depicted in Fig. 1. The lung thermal compartment (L) at temperature \( T_L \) is shown schematically in the upper portion of the figure. \( T_L \) has previously been proven to well represent systemic arterial temperature with a small transport delay of less than 3 s [17]. The PFC enters and exits the lung cyclically at an unsteady flow rate \( Q_F \) and a temperature \( T_F \). Before entering the lung compartment, the PFC transits through the thermal dead volume (\( V_D \)), analogous to physiological dead space, where heat exchange is negligible [10], [22]. The lung’s heat capacity (\( C_L \)) is the sum of the respective heat capacities of the PFC volume inside the lung (\( V_L \)), the extravascular lung water (EVLW) and the pulmonary blood volume (PBV). \( C_L \) is time varying since \( V_L \) varies as a function of PFC flow. The pulmonary circulation steadily enters and exits the lung compartment at the rate of the cardiac output (CO). The blood enters the lung compartment coming from the cardiac right ventricle at temperature \( T_v \), which corresponds to the temperature of systemic venous return (v). Then, blood exits the lung compartment at temperature \( T_L \).

The various heat transfers in the body are modeled as 7 parallel compartments representing the different perfused organs and tissues (lower portion of Fig. 1). The arterial blood at \( T_L \) is pumped by the heart into the seven compartments simultaneously. The modeled compartments are brain (br), heart (ca), digestive system (d), kidneys (k), fat (f), muscle (m) and other tissues such as skin and bone marrow (o). \( T_v \) is seen as a homogenous mix of body compartment temperatures depending on their respective perfusion. Muscular and metabolic heat production are neglected since the cooling occurs rapidly and the subject is paralyzed during TLV [17].
The complete continuous time-variant state-space model of the thermal model of Fig. 1 can be presented as:

\[
\dot{T}(t) = A(t)T(t) + B(t)u(t)
\]

where \(A(t)\) is time varying and defined in the matrix on the bottom of the page, \(T^T = [T_L \ T_{Br} \ T_{ca} \ T_d \ T_k \ T_f \ T_m \ T_o]\) and \(B(t)^T = [K_1(t) \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0]\), where \(T^T\) denotes the transpose.

The thermal dynamics of the inspired and expired PFC \((K_1(t))\) is defined as:

\[
K_1(t) = \begin{cases} 
\frac{Q_P(t) \rho_P c_P}{C_L(t)}, & \text{if } Q_P \geq 0 \text{ & } V_T(t) \geq V_D \\
0, & \text{otherwise},
\end{cases}
\]

where \(V_T\) represents the tidal volume, \(\rho_P\) the PFC density and \(c_P\) the PFC specific heat capacity. The PFC used is PFOB with \(c_P = 1065 \text{ J/kg/°C}\) and \(\rho_P = 1.93 \text{ g/mL}\).

The thermal dynamics of the pulmonary circulation \((K_2(t))\) is defined as:

\[
K_2(t) = \frac{COP_B c_B}{C_L(t)},
\]

where \(\rho_B\) represents the blood density and \(c_B\) the blood specific heat capacity. The thermal properties of the blood are: \(c_B = 3617 \text{ J/kg/°C}\) and \(\rho_B = 1.05 \text{ g/mL}\).

The lung’s thermal capacity at each instant can be calculated by:

\[
C_L(t) = \rho_P c_P V_L(t) + \rho_B c_B (EVLW \ + PBV).
\]

The thermal time constants of each body compartment can be modeled as:

\[
\tau = \frac{K_m c}{K_B CO \rho_B c_B}
\]

where \(m\) represents the ventilated subject mass, and \(K, K_B\) and \(c\) respectively correspond to the mass proportion, perfusion and thermal capacity of each thermal compartment. These constants were found in the literature and are presented in Table I for every compartment of both the ovine and human models. The non-perfused tissue and body content such as bone and gastrointestinal content presented in [24] were respectively distributed in the fat, the muscle and the other compartments according to their mass ratio such that the sum of \(K\) yields 100%.

### B. Cycle-by-Cycle Model

A schematic representation of the continuous and discrete time models are presented in Fig. 2. The continuous time-variant model of equation (1) is first sampled at sampling time \(t_e\) (\(t = kn \ t_e\)) where \(k\) is the discrete time of a respiratory cycle, \(n\) is the decimation factor between the discrete times \(i\) and \(k\) (\(i = kn + m\) with \(m = 0, 1, \ldots, n - 1\)). For this purpose, the time-varying matrices are approximated as time constant matrices during the sampling time: \(A(t) \approx A(t_e)\) and \(B(t) \approx B(t_e)\) for \(t \in [t_e; (i + 1) t_e]\). Consequently, the discrete time state-space model is:

\[
T_{k+1} = A_k T_k + B_k u_k.
\]

The matrices \(A_k\) and \(B_k\) at each cycle \(k\) are defined as:

\[
A_k = \prod_{i=k}^{k+n-1} e^{A(i t_e) t_e}
\]
Fig. 2. Schematic representation of the continuous time-invariant model and the discrete time-varying model.

and

\[ B_k = \sum_{n=0}^{k+n-2} \prod_{i=k}^{n-1} e^{A(i+1)t_e} B(i,t_e) t_e 
+ B((kn + n - 1)t_e) t_e. \] (8)

This cycle by cycle model allows computing the temperature in each compartment once every cycle without the necessity of computing the temperature at each instant when such precision is not necessary or when the computation time needs to be decreased.

C. Direct Optimal Control problem

Considering the initial conditions and the constraints, the control problem is to find the optimal command \( u(t) \) for \( t \in [0; t_f] \). The problem is thus an optimal control problem. With the direct optimal control method, this problem is equivalent to finding the command vector \( U = [u_0, u_1, ..., u_k, ..., u_{n-1}]^T \) which minimizes the cost function:

\[ J(U) = \sum_{k=1}^{k=t_f/t_e-1} (T_{ref} - T_{Lk})^2 + \beta (u_k - u_{k-1})^2 \] (9)

where \( T_{ref} \) is the targeted core body temperature and \( t_f \) the TLV duration. The first part of the cost function is the error between the reference temperature and the lung temperature. The second part of the cost function is a penalization of command increase by a factor \( \beta \).

The optimal control problem becomes a nonlinear optimization problem of the form:

\[ U_{opt} = \arg \min_U J(U), \] (10)

with \( u_k = T_{P_k} \) where \( T_{P_k} \in [T_{P_{min}}, T_{P_{max}}] \).

III. ANIMAL EXPERIMENTATION

A. Inolivent Liquid Ventilator Prototype

The liquid ventilator prototype developed by the Inolivent research team in Sherbrooke University (Sherbrooke, Quebec) is schematically shown in Fig. 3. Two independent volumetric piston pumps are used for cyclic inspiration and expiration of the PFC with four pinch valves synchronized to guide the PFC flow in order to renew a tidal volume of PFC into the lung. The ventilator is connected to the animal’s endotracheal tube by a Y-connector. The inspired PFC arrives cyclically from the reservoir at temperature \( T_P \). After expiration, the PFC returns to the oxygenator where it is oxygenated and temperature controlled. The oxygenator comprises 4 columns: columns #1 and #4 are made of thin stainless steel and each has a flexible heater affixed thereto to heat the PFC. Columns #2 and #3 of the oxygenator are built with a double wall. The exterior wall consists of polycarbonate and the inner cylinder is made of thin stainless steel. Water flowing within the double wall is used as a heat carrier for cooling the PFC inside the columns.

B. Animal Experimentation Protocol

The experimentation protocol was approved by the institutional Ethics Committee for Animal Care and Experimentation of the Sherbrooke University. The adult sheep (\( m = 61 \) kg) was sedated, orally intubated and restrained in supine position. The sheep was then anesthetized and ventilated with a conventional mechanical ventilator (Servo 300, Siemens, Sweden) in a pressure-regulated volume-controlled mode with a positive end expiratory pressure of 5 cmH\textsubscript{2}O. A rumenotomy (rumen surgically incised) was performed to avoid rumen meteorism and subsequent hemodynamic and respiratory impairment.

A femoral arterial catheter (PV2013L07, Pulsion Medical System, Germany) was installed for experimental temperature (\( T_L \) exp) and pressure recording (\( AP \)). Blood samples were also drawn from this catheter for analysis. A Swan Ganz thermodilution catheter (131F7P, Edwards Lifescience, USA) was inserted into the pulmonary artery for experimental temperature
TABLE II
HEMODYNAMIC, VENTILATORY AND PHYSIOLOGICAL RESULTS AT THE BASELINE AND AFTER ULTRAFAST HYPOTHERMIA INDUCTION BY TLV (30 MIN POSTBASELINE) IN THE 61-KG SHEEP

<table>
<thead>
<tr>
<th>Parameters</th>
<th>CMV</th>
<th>TLV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_m$ (°C)</td>
<td>37.9</td>
<td>32.3</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>115</td>
<td>94</td>
</tr>
<tr>
<td>$f$ (breaths/min)</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>$V_E$ (mL/min/kg)</td>
<td>100</td>
<td>68</td>
</tr>
<tr>
<td>EELV (mL/kg)</td>
<td>491</td>
<td>257</td>
</tr>
<tr>
<td>$P_{aO_2}$ (mmHg)</td>
<td>52.4</td>
<td>33.1</td>
</tr>
<tr>
<td>$P_{aCO_2}$ (mmHg)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>pH</td>
<td>7.27</td>
<td>7.40</td>
</tr>
<tr>
<td>APM (mmHg)</td>
<td>103</td>
<td>103</td>
</tr>
</tbody>
</table>

$T_L$: Arterial temperature, HR: Heart Rate, $f$: Respiratory rate, $V_E$: Minute ventilation, EELV: End Expiratory PFC volume, $P_{aO_2}$ and $P_{aCO_2}$: Oxygen and carbon dioxide partial pressure and APM: Mean arterial pressure.

D. Sheep Thermal Model Parameters

Table III presents the physiological model parameters measured and calculated in vivo for the sheep. EVEL, PBV and CO were measured by the transpulmonary thermodilution method. For an adult sheep, $V_D$ varies as 4.8 ±1.7 mL/kg [26]. For this experiment, $V_D$ was determined to be 3.4 mL/kg for a good fit of the model. The lower portion of the table shows the time constants for each body compartment from equation (5). The brain, heart, digestive (liver, stomach, intestine, spleen) and kidneys all displayed rapid thermal dynamics with $\tau \leq 130$ s. Fat, muscle, skin and other compartments displayed slow thermal dynamics with a time constant ranging from 21 min to over 33 min. This was likely related to the higher time constant of these compartments.

Fig. 4 depicts the ventilation profile and the lung thermal capacity for the first 20 min of the experimentation. The ventilatory frequency rose from 5.5 to 6.5 breath/min and tidal volume from 480 mL to 600 mL which is standard for TLV (Fig. 4(a) and (b)). The lung thermal capacity depicted in Fig. 4(c) started at 2.8 kJ/°C prior to TLV due to EVEL and PBV, and oscillated between 4.8 and 7.6 kJ/°C synchronized with PFC lung volume during TLV.

E. Optimal Hypothermia Induction in Sheep

The a posteriori computation of the optimal inspired PFC temperature using the direct optimal control was performed using the results of the experimentation in the adult sheep (Table III and Fig. 4). The penalization factor $\beta$ was set to 0.5 and the lower boundary $T_{P_{min}}$ was set to 11.0 °C. The targeted temperature $T_{ref}$ was 32 °C. The initial temperature of the subject was 37.9 °C such that every compartment temperature was

remained above 95% during the entire experiment. Heart rate (HR) in hypothermic TLV decreased by 20% compared to normothermic CMV. $P_{aO_2}$, $P_{aCO_2}$ and pH all exhibited standard values confirming that ventilation was adequate during CMV and TLV, even if minute ventilation ($V_E$) decreased in TLV. The lower $V_E$ was caused by the lower respiratory rate ($f$) since the PFC is denser and more viscous than air. Mean systemic arterial pressure (APM) remained the same during both phases.

C. Experimentation Results

Table II shows the results of the ventilatory parameters and of the blood gas analysis for the sheep at the baseline for both CMV and hypothermic TLV. Arterial oxyhemoglobin saturation monitoring ($T_e$ exp). Cold saline injections for transpulmonary thermodilution tests were performed in the right jugular vein. The PiCCO and VoLEF devices (Pulsion Medical Systems, Germany) were used to perform the test analyses [25]. Accuracy of measured blood temperature is ±0.1 °C as per the Pulsion Medical System product information. In addition, a thermistor temperature sensor (402AC, Measurement Specialties, USA) was inserted in the rectum at a depth of 7 cm. In the thermal model, the rectal temperature is analogous to the muscle compartment temperature which is the slowest body temperature to vary ($T_m$ exp) [17].

After a 30-min recovery period at 100% $O_2$ and at normothermia (38 °C), the sheep was paralyzed by curarization and shifted from conventional mechanical ventilation (CMV) to TLV. A filling volume of 15 mL/kg preoxygenated PF0B at 11 °C was instilled in the sheep’s lungs. End expiratory lung PFC volume (EELV) was gradually raised to 30 mL/kg in the first 5 min, maintained at 30 mL/kg for 10 min then decreased to 20 mL/kg and finally maintained until stabilization of all temperatures. Both inspiration and expiration were volume-controlled, pressure-limited and time-cycled. The inspired PFC temperature was manually controlled by the user to achieve a targeted core temperature of 32 °C. Arterial oxygen saturation of hemoglobin was continuously monitored using pulse oximetry (Radical, Masimo, USA) via a sensor attached to the tongue.

Prior to shifting to TLV, three transpulmonary thermodilution tests were performed to determine $PBV$, EVELW and CO. The ventilatory parameters and the heart rate were recorded at the end of the baseline in CMV and after mild hypothermia induction by TLV after temperature stabilization. Blood samples were concomitantly drawn for $P_{aO_2}$, $P_{aCO_2}$ and pH analysis (Rapidlab, Siemens, United Kingdom). The latter were temperature corrected according to femoral arterial temperature.
Experimental measurements of (a) PFC flow in the lung ($Q_P$), (b) PFC volume in the lung ($V_L$), and (c) lung thermal capacity ($C_L$) during the first 20 min of TLV in the adult sheep.

Fig. 4. Experimental measurements of (a) PFC flow in the lung ($Q_P$), (b) PFC volume in the lung ($V_L$), and (c) lung thermal capacity ($C_L$) during the first 20 min of TLV in the adult sheep.

set to this temperature prior to TLV. The time discretization $t_e$ of the model was set to 0.02 s (50 Hz). The direct optimal control solution was found for a TLV duration of 30 min ($t_f = 30$ min). Optimization took 24.1 s to find a solution with a 2.0 GHz Intel Core™ i7 processor with 6 GB of memory. The developed cycle-by-cycle model drastically reduced the computation time. It took approximately 24 s to compute a solution compared with more than 24 h when using the continuous time-varying model.

Fig. 5 presents the results from the animal experimentation measurements ($T_L$ exp, $T_v$ exp, $T_m$ exp and $T_P$ exp), the simulation of the mathematical model ($T_L$ opt ctrl, $T_v$ opt ctrl, $T_m$ opt ctrl and $T_P$ opt ctrl). $T_L$ exp compared to simulated $T_L$ opt ctrl, $T_v$ exp compared to simulated $T_v$ opt ctrl, and $T_m$ exp compared to simulated $T_m$ opt ctrl were very similar as seen in Fig. 5(a)–(c), thus illustrating the accuracy of the model. The optimized inspired PFC temperature computed by the simulator in Fig. 5(c) reveals that the PFC should have been maintained at 11 °C for 2.3 min and heated from 11 to 28 °C in 10 min. With this optimal control, $T_L$ would have stabilized at approximately 32 °C and would have thus avoided undershooting.

Table IV presents the settling lung temperature ($T_s$ L), the time to reach 34 °C ($t_h$) for every compartment, the undershoots of lung temperature under 32 °C ($M$) of lung temperature and the cost function $J$ calculated for the direct optimal control as well as the simulated experimentation results. With the optimal control, a similar time was needed for $T_L$ to reach mild hypothermia compared to the model results with no observed overshoot. In fact, lung temperature reached 34 °C during the filling phase at the beginning of TLV. When looking at the $t_h$ for the fast dynamic compartments, the cooling speed of vital organs was closely similar between the a posteriori computed optimal temperature and the experimental inspired temperature. The $t_h$ for the slow dynamic compartments was slightly longer when the undershoot was avoided (11 to 36% longer). In both cases, whole body hypothermia was reached in less than 35.9 min (−6.7 °C/h). The cost function was reduced (88%) using the

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Optimal Control</th>
<th>Simulated Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_s$ L (°C)</td>
<td>32.0</td>
<td>31.7</td>
</tr>
<tr>
<td>$t_h$ (s)</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>$M$ (°C)</td>
<td>0.0</td>
<td>−2.1</td>
</tr>
<tr>
<td>$t_b$ (min)</td>
<td>4.0</td>
<td>3.1</td>
</tr>
<tr>
<td>$t_a$ (min)</td>
<td>2.8</td>
<td>2.9</td>
</tr>
<tr>
<td>$t_c$ (min)</td>
<td>1.1</td>
<td>1.3</td>
</tr>
<tr>
<td>$t_d$ (min)</td>
<td>2.5</td>
<td>2.6</td>
</tr>
<tr>
<td>$t_k$ (min)</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>$t_f$ (min)</td>
<td>23.3</td>
<td>15.2</td>
</tr>
<tr>
<td>$t_m$ (min)</td>
<td>35.9</td>
<td>25.5</td>
</tr>
<tr>
<td>$J$ (°C/h)</td>
<td>$0.4 \times 10^5$</td>
<td>$3.2 \times 10^5$</td>
</tr>
</tbody>
</table>

Fig. 5. (a) Lung temperature ($T_L$), (b) venous temperature ($T_v$), (c) muscle temperature ($T_m$), and (d) inspired PFC temperature ($T_P$) from experimental results (exp), simulated results, and computed direct optimal control (opt ctrl) in the sheep.

TABLE IV

SETTLING LUNG TEMPERATURE ($T_s$ L), TIME NEEDED TO ACHIEVE MILD HYPOTHERMIA ($t_h$), UNDERSHOOT UNDER $M_a = 32$ °C FOR LUNG TEMPERATURE ($M$), AND COST FUNCTION ($J$) FROM SIMULATIONS USING BOTH THE COMPUTED OPTIMAL PFC TEMPERATURE AND THE EXPERIMENTAL INSPIRED PFC TEMPERATURE DURING ULTRAFAST MILD HYPOTHERMIA INDUCTION BY TLV IN THE SHEEP
direct optimal control, mostly due to the absence of the undershoot.

IV. SIMULATION OF ADULT HUMAN MODEL

A. Human Thermal Model Parameters

The physiological parameters for the human adult are presented in Tables I and V. The physiological parameters of the model obtained directly from the literature are presented in the upper portion of Table V with their respective references. Using Table I and equation (5), we determine the thermal time constants of all compartments. They are presented in the lower portion of Table V.

Using these physiological parameters, the parametric thermal model presented in equations (1) and (6) can be adapted to humans, and the optimal control problem becomes a nonlinear optimization problem in the form of equation (10), exactly as for the ovine model, but now with the human thermal model. Using this information, the constraint \( u_k \geq T_{P_{\text{min}}} \) and the initial condition as the normothermic temperature for humans (37 °C), it is possible to compute the optimal inspired PFC temperature for rapid hypothermia induction by TLV in clinical applications.

B. Optimal Hypothermia Induction in a Human Adult Model

The computation of the optimal inspired PFC temperature for a normal 61 kg adult human was performed using the ventilatory profile of the experimentation in the adult sheep presented in Fig. 4. The lower boundary \( T_{P_{\text{min}}} \) and the targeted temperature \( T_{\text{ref}} \) were maintained at respectively 11 °C and 32 °C as in the sheep. The initial temperature of the subject was set to 37 °C. The discretization time \( t_c \) of the model was maintained at 0.02 s (50 Hz) and \( T_{P} \) was found for 30 minutes of TLV.

Fig. 6 depicts an optimal hypothermia induction by TLV in an adult patient. The computed optimal inspired PFC temperature profile in Fig. 6(c) was similar to that of the sheep presented in Fig. 5(d). Indeed, the PFC was maintained at 11 °C for the first 3 min then heated to 28 °C around 10 min in both cases. In Fig. 6(a), \( T_{br} \) cooled promptly and reached hypothermia in the first 10 respiratory cycles. \( T_{m} \), representing the slowest compartment, took less than 20 min to reach hypothermia and was almost settled after 30 min of TLV (Fig. 6(b)). These cooling results demonstrate that the brain should indeed reach MTH in less than 10 min and the whole body in less than 30 min in the human model.

Table VI shows the performances of hypothermia induction in the adult human model. The whole body achieved mild hypothermia in 18.5 min (−9.7 °C/h) compared to 35.9 min (−6.7 °C/h) in the sheep (48% faster). This can be explained by the lower thermal time constant of the slow cooling compartments of the human subject compared to the sheep (Table III

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Human Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVLW (mL)</td>
<td>490 [25], [27]</td>
</tr>
<tr>
<td>I' EV1 (mL)</td>
<td>475 [28], [29]</td>
</tr>
<tr>
<td>Vp (mL)</td>
<td>200 [30], [31]</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>6.0 [32], [33]</td>
</tr>
<tr>
<td>( \tau_k ) (s)</td>
<td>100</td>
</tr>
<tr>
<td>( \tau_a ) (s)</td>
<td>74</td>
</tr>
<tr>
<td>( \tau_d ) (s)</td>
<td>177</td>
</tr>
<tr>
<td>( \tau_r ) (s)</td>
<td>15</td>
</tr>
<tr>
<td>( \tau_f ) (min)</td>
<td>13.6</td>
</tr>
<tr>
<td>( \tau_m ) (min)</td>
<td>19.8</td>
</tr>
<tr>
<td>( \tau_u ) (min)</td>
<td>6.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Optimal Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T_{br} ) L (°C)</td>
<td>32.0</td>
</tr>
<tr>
<td>( t_{br} ) L (s)</td>
<td>11</td>
</tr>
<tr>
<td>( M ) (°C)</td>
<td>0.0</td>
</tr>
<tr>
<td>( t_{br} ) v (min)</td>
<td>5.1</td>
</tr>
<tr>
<td>( t_{br} ) br (min)</td>
<td>2.5</td>
</tr>
<tr>
<td>( t_{br} ) ca (min)</td>
<td>1.9</td>
</tr>
<tr>
<td>( t_{br} ) k (min)</td>
<td>3.7</td>
</tr>
<tr>
<td>( t_{br} ) f (min)</td>
<td>0.4</td>
</tr>
<tr>
<td>( t_{br} ) m (min)</td>
<td>12.9</td>
</tr>
<tr>
<td>( t_{br} ) o (min)</td>
<td>18.5</td>
</tr>
<tr>
<td>( J ) (°C^2 s)</td>
<td>6.3</td>
</tr>
<tr>
<td>( J ) (°C^2 s)</td>
<td>0.4 \times 10^5</td>
</tr>
</tbody>
</table>

Fig. 6. (a) Lung temperature (\( T_{br} \)) and brain temperature (\( T_{m} \)). (b) venous temperature (\( T_{v} \)) and muscle temperature (\( T_{m} \)). and (c) inspired PFC temperature (\( T_{P} \)) computed with direct optimal control (opt ctrl) for a human adult \( V_D = 200 \text{ mL} \) and \( CO = 6 \text{ L/min} \).
vs. Table V) which is mostly caused by the CO (14% higher) and the higher perfusion of the slow cooling compartment. Moreover, normothermia is lower in humans compared to the sheep thereby decreasing the temperature gradient needed to achieve 34 °C.

### C. Sensitivity Analysis of the Human Thermal Model

A sensitivity analysis was performed for the human model to determine the most sensitive parameters on cooling performances. The optimal inspired PFC temperature depicted in Fig. 6(c) was kept constant and each parameter of Table V was changed using the one-factor-at-a-time method. Briefly, the method involves setting all parameters at their nominal values with every parameter changed one at a time by ±20% of its nominal value. Simulations were run for each parameter change and the slope was calculated to determine the local derivative (sensitivity) of each parameter.

Table VII shows the sensitivity of the physiological parameters during hypothermia induction by TLV in adult humans. The results present the effect on $T_L$, $t_h$, $t_{br}$, $t_{br}$ m, $M$ and $J$, as the local derivative of each parameter at its nominal value in percent. For example, a variation of −1% of $V_D$ from its nominal value will generate an undershoot (M) of −0.02 °C.

Table VII shows that the model is insensitive to EVLW and PBV. A variation in EVLW and/or PBV had negligible effect on $t_{br}$ and no effects on $T_L$, $t_h$, $m$, $M$ and $J$. Body compartment time constants have mostly negligible effects on hypothermia induction performances. $\tau_{br}$ and $\tau_m$ have effects on respectively $t_{br}$ and $t_h$ that was expected. For example, if the brain time constant ($\tau_{br}$) rises by 20% because of a perfusion problem, the brain will take an additional 26 seconds to achieve hypothermia. Hence, a 20% increase in $\tau_m$ would result in the whole body hypothermia being reached 3.4 min later. The loss of cooling speed is undesirable but MTH can still be induced in less than 10 min for the brain and less than 30 min for the whole body.

The two most sensitive parameters on cooling performances and safety of the method (arterial temperature undershooting) are the thermal dead volume and the cardiac output. For a variation of ±50 mL of $V_D$ (±25%), which appears reasonable [31], cooling performances vary significantly. $t_h$ varies by ±2.5 min for the whole body and ±28 s for the brain when $V_D$ varies by ±25% while the undershoot reaches −0.5 °C if $V_D$ decreases by 25%.

The method is sensitive to cardiac output and in addition, cardiac output can vary widely from one patient to another. Moreover, in the application of hypothermia induction by TLV in post-cardiac arrest patients, the cardiac output can vary as much as from 3 to 8 L/min (−50% to +33%) depending on the condition of the patient and type of disease [32]. Table VII shows that the worst-case scenario (i.e. the biggest arterial temperature undershoot) is a combination of low cardiac output and low thermal dead volume.

### D. Worst-Case Optimal Control

The direct optimal control algorithm was used to compute the worst-case optimal control (WCOC) of inspired PFC temperature for a human. The WCOC was computed with $V_D = 150$ mL and $CO = 3$ L/min. Using thus computed WCOC-inspired PFC temperature profile ensured the avoidance of arterial temperature undershoot irrespective of the patient’s $CO$ or $V_D$.

Fig. 7 shows the human model results of the optimal hypothermia induction by TLV with normal physiological parameters (Table V) using the computed WCOC-inspired PFC temperature profile (Fig. 7(c)). The main differences with Fig. 6(c)
are the higher initial PFC temperature and faster rewarming of the latter. Using the WCOC-inspired temperature profile, lung and brain temperatures still cooled promptly, i.e., within the first 5 min to reach 34 °C, but took longer to reach 32 °C (Fig. 7(a)). The slow dynamics compartment (Fig. 7(b)) cooled slower using the computed WCOC profile whereas the whole body still reached hypothermia in approximately 26 min.

Fig. 8 displays isolines of $t_b$, $m$, $t_b$, $br$ and $T_s$ as a function of a $CO$ varying from 3 to 8 L/min, and a $V_D$ of 150 to 250 mL. Fig. 8(a) shows that the time needed to reach whole body hypothermia can take up to 40 min if $CO$ is very low (near 3 L/min) and $V_D$ is large, although patients with normal $CO$ (over 5 L/min) and normal $V_D$ (200 mL or less) should reach hypothermia in less than 30 min. Fig. 8(b) depicts that most of the time, hypothermic neuroprotection begins within the first 6 minutes of TLV and in the worst cases, hypothermia is reached within 10 min for the brain. When using the WCOC-inspired temperature profile, the settling temperature remained in the range of $\pm 0.25$ °C of the targeted temperature for all patients (Fig. 8(c)).

V. DISCUSSION

The main purpose of this work was to develop a method to extrapolate ultrafast MTH induction by TLV in adult human model from adapting physiological parameters of a thermal model of ovines. To our knowledge, this is the first study showing an ultrafast MTH induction by TLV in sheep or any other large adult animal, and the first projection to the human model.

In the ovine results presented here, the simulated $T_L$, $T_v$, and $T_m$ compared to the experimental $T_L$, $T_v$ and $T_m$ traces showed a good fit of the thermal model justifying its use with its parameters for computing the optimal control. The experimental results of the model presented in only one adult sheep is a limitation of our study. However, the parametric lumped thermal model was previously validated in two groups of differing weights, namely 6 newborn lambs (2–6 kg) and 6 juvenile ovines (20–24 kg) [17]. Since it’s a parametric model, the upscale of the parameters to 61 kg should not incur any changes in the mathematical structure because all compartments remain the same from newborns to adults. Moreover, the upscale between newborn and juvenile is known to display a larger physiological change than the upscale from juveniles to adults [24]. At this stage, there was no interest for us to collect experimental data of a group of adult animals to study the variability during MTH induction by TLV but such study is planned to be performed in the near future. TLV in large animals (over 35 kg) was previously performed in a group of 10 sheep (53 ± 4 kg) in normothermia for 24 hours with an acute respiratory distress syndrome [34].

The projection to adult humans allows computing the optimal PFC temperature in order to induce safe and rapid hypothermia by TLV. The simulated results revealed that optimal inspired PFC temperature was similar between the sheep and the human model. This is due to the analogous features of the mathematical models (same order, same mathematical structure, comparable parameters). However, the simulation strongly suggests that cooling is faster in humans. For the same weight, cooling performances were different between the two species which is well represented by the time constants higher in Table III for the sheep compared to those in Table V for the human model. This means that the cooling performances can be expected to be better in humans ($-10$ °C/h) than in sheep ($-7$ °C/h). This also indicates that the efficiency of the method is sensitive to the physiological parameters.

In the ovine experimentation, the optimal control showed that the initial PFC temperature was soundly chosen but that the heating profile was not optimal. PFC should have been maintained longer at a lower temperature and subsequently heated faster to avoid undershoot. The experimental results revealed that arterial temperature reached 29.7 °C (M = 2.3) which is way below the targeted 32 °C, and even below the critical temperature of 30 °C which can cause cardiac arrhythmia [18]. Even if no cardiac arrhythmia was observed during the experimentation, the constraint to avoid undershoot of the temperature under the critical temperature was not respected thus leading to safety issues. Conversely, the cooling performances of the computed optimal inspired PFC temperature was acceptable: there was no issue regarding safety. Hence, the mathematical model allows the existence of an optimal command without undershoot. Alternatively, a solution to increase the cooling speed of the whole body while remaining safe could be to adjust the cost function in order to minimize the quadratic error between $T_{ref}$ and $T_m$ while constraining $T_L$ over 30 °C or to another temperature considered safe for the heart.
For a practical implementation of the presented method, an inspired PFC temperature profile according to the targeted patient temperature and patient parameters could be efficiently computed with the developed discrete time-cycled model. The liquid ventilator control unit would drive the heat exchanger to track the computed PFC temperature profile. Moreover, the optimal command can only be adequately computed if all parameters are perfectly known. In practice, the TLV ventilatory profile, the PFC filling volume, $EELV$, $Q_p$, $V_D$ and $f$ would all be defined by the attending clinicians. This does not present an issue since all of these ventilatory parameters are known in real time [35]. Hence, it is possible to develop an algorithm or a precalculated table to update the computed inspired PFC temperature in spite of modifications in ventilatory parameters.

In practice, the real problems will stem from the unknown parameters. The parametric uncertainties allow highlighting parameters that deteriorate the safety or efficiency of the optimal command. The two most sensitive and potentially highly variable parameters are the thermal dead volume and the cardiac output. For this reason, a worst-case optimal control of PFC temperature was computed with the lowest $CO$ and $V_D$. In this manner, every eligible patient for MTH induction by TLV would avoid arterial temperature undershooting regardless of their physiological parameters. Therefore, the use of the WCOC-inspired PFC temperature profile slightly deteriorates the cooling performances although safety is ensured. Moreover, when using the WCOC-inspired PFC temperature profile, the brain temperature in all patients reached MTH in less than 10 min thus meaning that neuroprotection begins shortly after the beginning of TLV regardless of the patient’s physiological parameters. This observation gives one explanation of the higher neuroprotection observed in animal experimentation while ultrafast cooling by TLV is used in post-cardiac arrest patient [2]. Moreover, results in Tables III and V shows that all other vital organs (i.e. heart, liver and kidneys) have rapid thermal dynamics and will reach therapeutic hypothermia quickly leading to multi-organ protection, as observed experimentally [36].

Beside the use of the WCOC, another means to manage the risks could be to consider the on-line measurement of lung temperature. A previous study has shown that this temperature can be measured using a delocalized lung temperature sensor and confirmed that it is closely correlated with femoral arterial temperature [37]. Hence, it could be possible to use this information to develop a robust feedback control strategy or a state machine, instead of a feedforward strategy. Moreover, measurement of $CO$ and $V_D$ during TLV could be used to adapt the model in real time so the optimal inspired PFC temperature could be recomputed. While measurement of the physiological parameters is not possible, an on-line identification algorithm could be implemented to estimate the model parameters in real time by using some body temperature measurements. This could lead to the implementation of adaptive or predictive control [38], [39].

The present study has demonstrated that a liquid ventilator can be used to precisely control the inspired PFC temperature to efficiently control the lung temperature and the cooling of the organs. With such a liquid ventilator, post-cardiac arrest patients could be promptly cooled in less than 30 min upon their arrival at the hospital, or in the ambulance during transport to hospital, to dramatically improve neuroprotection and survival rate [36]. Even if the ultrafast MTH induction of post-cardiac arrest patients seems the most promising application of TLV, a previous study has shown that the liquid ventilator can also be used to maintain a targeted core temperature precisely or to control slow posthypothermic rewarming with a precision of ±0.1 °C/h [37].

VI. Conclusion

The ultrarapid cooling of the pulmonary circulation while performing TLV requires an optimal control to ensure efficiency and safety of the method. In the present study, a direct optimal control was designed to compute the optimal inspired PFC temperature for swift hypothermia induction while avoiding thermal undershoot. The computed optimal control in an adult sheep revealed that the inspired PFC temperature profile could have been improved to avoid arterial temperature undershoot to ensure a safe induction of MTH. The projection to adult humans indicates that the cooling performances should at least be equivalent or even better than the preclinical ovine results. The human model predicts a cooling speed of $-10$ °C/h for the whole body and $-72$ °C/h for the brain. A sensitivity analysis on the parameters of the adult human model revealed that uncertainties of the thermal dead volume and the cardiac output had major effects on the undershoot and on the cooling time of the organs. This high sensitivity of the thermal dead volume and cardiac output leads to recommend the computation of a worst-case optimal control of inspired PFC temperature to ensure patient safety. Thus, even if the worst-case optimal control decreases the cooling performances that could be achieved in patients with normal $CO$ and $V_D$, brain temperature would reach neuroprotection in maximum 10 min ($-18$ °C/h) for all patients. Altogether, the present findings highlight the feasibility of the clinical use of a liquid ventilator for ultrafast mild therapeutic hypothermia induction, thereby potentially improving the quality of life and survival of post-cardiac arrest patients.

ACKNOWLEDGMENT

The authors would like to thank Dr. R. Robert for his help with the design of the liquid ventilator technology.

REFERENCES


Author’s photographs and biographies not available at the time of publication.