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Brain Cooling With Ventilation of Cold Air Over Respiratory Tract in Newborn Piglets: An Experimental and Numerical Study

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ABSTRACT We investigate thermal effects of pulmonary cooling which was induced by cold air through an endotracheal tube via a ventilator on newborn piglets. A mathematical model was initially employed to compare the thermal impact of two different gas mixtures, O_2-medical air (1:2) and O_2-Xe (1:2), across the respiratory tract and within the brain. Following mathematical simulations, we examined the theoretical predictions with O_2-medical air condition on nine anesthetized piglets which were randomized to two treatment groups: 1) control group ($n = 4$) and 2) pulmonary cooling group ($n = 5$). Numerical and experimental results using O_2-medical air mixture show that brain temperature fell from 38.5 °C and 38.3 °C ± 0.3 °C to 35.7 °C ± 0.9 °C and 36.5 °C ± 0.6 °C during 3 h cooling which corresponded to a mean cooling rate of 0.9 °C/h ± 0.2 °C/h and 0.6 °C/h ± 0.1 °C/h, respectively. According to the numerical results, decreasing the metabolic rate and increasing air velocity are helpful to maximize the cooling effect. We demonstrated that pulmonary cooling by cooling of inhalation gases immediately before they enter the trachea can slowly reduce brain and core body temperature of newborn piglets. Numerical simulations show no significant differences between two different inhaled conditions, i.e., O_2-medical air (1:2) and O_2-Xe (1:2) with respect to cooling rate.

INDEX TERMS Pulmonary cooling, brain, piglet, numerical simulation, bio-heat transfer.

I. INTRODUCTION

Mild hypothermia ($HT_{32–35°C}$) is an effective neuroprotective strategy for a variety of acute brain injuries including birth asphyxia [1]. Birth asphyxia causes approximately 23% of all neonatal deaths worldwide [2]–[4]. Studies indicate that one in six children potentially would benefit from brain hypothermia; hence the rate of death and disabilities is unacceptably high [3]. Recently, it has been shown that neuroprotection significantly increased from ∼35% with surface cooling alone to ∼70% when cooling was combined with 50% inhaled nontoxic anesthetic gas Xenon (Xe) [5]. The major disadvantage of this intervention is that Xe is very expensive and its administration is rather complicated, since it requires intubation and ventilation of the patient as well as a large volume of expensive Xe gas. Dingley *et al.* developed a relatively straightforward rebreathing closed circuit system for cost effective delivery of Xe to mechanically ventilated neonates as a potential neuroprotectant after perinatal asphyxia [6].

Among various methods of induced hypothermia, body surface cooling is the one of the most commonly used at the bedside. However, is not always applicable in a clinical setting because of the relatively large surface area of the human body and systemic complications introduced by surface cooling that may be difficult to control [7]. Based on the anatomical features and effectiveness of pulmonary architecture and its intimate contact with the entire cardiac output, lung and pulmonary circulation may act as an *in-vivo*

heat exchanger, such that heat can move from the blood to the alveolar space and then to the environment [8], [9], and [10]. In the present study, we test the hypothesis that breathing cold air over the respiratory tract can reduce brain temperature. We took advantage of advances in the numerical modeling of heat and water vapor transport in tissues to predict brain temperature during pulmonary cooling with two different air conditions, i.e., O_2-medical air (1:2) and O_2-Xe (1:2) using Pennes' heatsink model. These data are difficult to acquire in clinical settings due to the cost and scarcity of Xe as well as the difficulty in justifying invasive measurements of brain tissue temperature. In addition, we have investigated the effect of some physiological parameters across the respiratory tract through numerical simulation. Following numerical simulations, we examined the theoretical predictions in anesthetized piglets to investigate the effects of cold gas (O_2-medical air) introduced through an endotracheal tube on brain temperature; we concurrently measured similar physiological parameters during the *in-vivo* experiments.

II. MATERIALS AND METHODS

A. THEORETICAL MODEL

Analysis of heat and water transport processes in the respiratory tract is a difficult task because the flow patterns inside this area are rather complex. The airway can be idealized as a long, right circular cylinder structure [11], which simplifies the theoretical analysis. Schematic diagram of the airway model is shown in Figure 1.

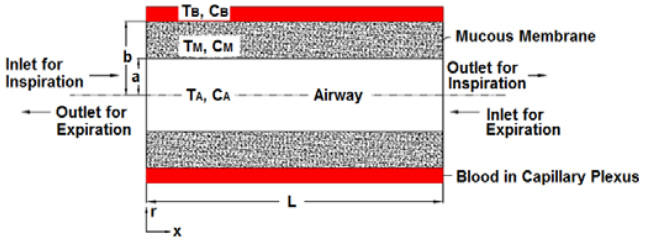

FIGURE 1. Schematic diagram of the airway model.

Based on the well-known Pennes bioheat transfer equation, the balance of the energy in the tissue between heat conduction through cellular tissue, heat convection by flow of blood and heat production due to cellular metabolism results as follows:

$$\rho c\frac{\partial T}{\partial t} = k\nabla^2 T + \omega_b c_b(T_b - T) + Q \qquad (1)$$

where $\rho(\mathrm{kg{\cdot}m^{-3}})$, $c(\mathrm{J{\cdot}kg^{-1}{\cdot}{^\circ}C^{-1}})$, and $k(\mathrm{W{\cdot}m^{-1}{\cdot}{^\circ}C^{-1}})$ are the density, specific heat, and thermal conductivity of tissue, $T(^\circ\mathrm{C})$ is the local tissue temperature, $t(\mathrm{s})$ is the time, $\omega_b(\mathrm{kg{\cdot}m^{-3}{\cdot}s^{-1}})$ is the volumetric blood perfusion rate, $c_b(\mathrm{J{\cdot}kg^{-1}{\cdot}{^\circ}C^{-1}})$ is the specific heat of blood, $T_b(^\circ\mathrm{C})$ is the supplying arterial blood temperature and $Q(\mathrm{W{\cdot}m^{-3}})$ is the metabolic heat generation rate.

At the mucous-air interface ($r = \mathrm{a}$), the boundary condition for the heat transfer is generally composed of two parts, i.e., convection and evaporation. At the entrance of the nasal cavity ($x = 0$), the continuity of heat flux is imposed as a convective boundary condition. An adiabatic condition was implemented at both deep tissue ($r = \mathrm{b}$) and the end of human respiratory tract ($x = L$) due to the relatively lower temperature gradient between two layers. The boundary conditions can be written as follows [11]

$$k\frac{\partial T}{\partial r} = h(T - T_A) + 0.001 H M_m(P_t^* - \varphi P_f^*) \quad r = a \qquad (2)$$

$$\frac{\partial T}{\partial r} = 0 \quad r = b \qquad (3)$$

$$k\frac{\partial T}{\partial x} = h'(T - T_{in}) \quad x = 0 \qquad (4)$$

$$\frac{\partial T}{\partial x} = 0 \quad x = L \qquad (5)$$

where $T_{in}(^\circ\mathrm{C})$ is the breathing air temperature and $T_A(^\circ\mathrm{C})$ is the axial air temperature in the flowing air stream, $h'(\mathrm{W{\cdot}m^{-2}{\cdot}{^\circ}C^{-1}})$ is the apparent heat convection coefficient between the tissue and the breathing air, $h(\mathrm{W{\cdot}m^{-2}{\cdot}{^\circ}C^{-1}})$ is the heat convection coefficient between the mucosal surface and the flowing airstream for each air stream, i.e., O_2-medical air and O_2-Xe [12]. Table 1 compares the thermal properties of O_2-medical air and O_2-Xe [13].

TABLE 1. Physical properties of O_2-medical air and O_2-Xe at normal atmospheric pressure.

		O_2-medical air(1:2)	*O_2-Xe(1:2)*
Density	$(\mathrm{kg.m^{-3}})$	*1.5*	4.014
Specific Heat	$(\mathrm{J.kg^{-1}.{^\circ}C^{-1}})$	900	246
Thermal Conductivity	$(\mathrm{W.m^{-1}.{^\circ}C^{-1}})$	*0.021*	*0.010*

φ is the relative humidity of flowing air from the ventilator, $H(\mathrm{J{\cdot}kg^{-1}})$ is the latent heat of water vapor, $M_m(\mathrm{kg{\cdot}s^{-1}{\cdot}m^{-2}{\cdot}Pa^{-1}})$ is the water penetrative coefficient in the mucosal surface, $P_f^*(\mathrm{Pa})$ is the saturated vapor pressure at breathing air temperature and $P_t^*(\mathrm{Pa})$ is the saturated vapor pressure at tissue temperature which can be calculated as follows [14]:

$$\ln(P^*) = \frac{c_1}{T} + c_2 + c_3 T + c_4 T^2 + c_5 T^3 + c_6 \ln(T) \qquad (6)$$

where *ln* is the natural logarithm and $P^*(\mathrm{Pa})$ is the water saturated pressure [14]. The regression coefficients c_1 to c_6 used in this study were taken from the literature so that Eq. (6) yields pressure P^* in Pa on condition that temperature T is provided in Kelvin [14]. In the respiratory tract, the energy balance equation for the air in the x direction can be defined as [11]:

$$\rho_A C_A\left(\frac{\partial T_A}{\partial t} + u\frac{\partial T_A}{\partial x}\right) = \frac{S}{A}\left(h\,(T - T_A) + 10^{-6} H M_m(P_t^* - \varphi P_f^*)\right) \qquad (7)$$

where $C_A(\mathrm{J{\cdot}kg^{-1}{\cdot}^{\circ}C^{-1}})$ and $\rho_A(\mathrm{kg{\cdot}m^{-3}})$ are the specific heat and density of the air at each condition, $S(\mathrm{m^2})$ and $A(\mathrm{m})$ are the local airway cross-section and perimeter and $u(\mathrm{m{\cdot}s^{-1}})$ is the mean longitudinal air velocity. P_a^* and P_t^* are saturated vapor pressure at surrounding air and tissue temperature, respectively. The air temperature gradients in the axial direction are usually much smaller than those in the radial direction. Correspondingly, the axial conduction is neglected here for simplicity. Moreover, radial conduction $(\partial T_A/\partial r)$ is equally negligible with respect to convective heat transfer, i.e., $u(\partial T_A/\partial x)$. During the inspiration and expiratory phases of the breathing cycle, the axial inlet $(x = 0)$ boundary condition is considered as the ventilator air temperature $(T_A = T_{in})$ and zero heat flux $(\partial T_A/\partial x = 0)$ is imposed at the end of the human respiratory tract $(x = L)$ due to slight temperature change in x direction at this boundary. The energy balance for the blood and tissue is defined by conduction in the tissue and convection in the blood as follows:

$$\mathrm{k}\frac{(\mathrm{T_m\,(x,a,t) - T_m\,(x,b,t))}}{(\mathrm{b-a})} = \mathrm{h_{bt}\,(T_m\,(x,b,t) - T_b\,(x,t))} \quad (8)$$

where h_{bt} is the heat convection coefficient between blood and tissue, $a(\mathrm{m})$ is the radius of respiratory tract, $b(\mathrm{m})$ is the external radius of the calculation domain and $k(\mathrm{W{\cdot}m^{-1}{\cdot}^{\circ}C^{-1}})$ is the thermal conductivity of tissue. Numerical simulation was applied to solve the above equations and calculate the thermal impact of inhaled cold air to the mucous membrane and blood temperature. Brain tissue temperature was then predicted using the mathematical model of temperature distribution in Eq. (1) for the brain tissue parameters [15], [16]. Due to the axisymmetry of the tissue geometry and the thermal load, only a 2D axisymmetric cylindrical domain (Fig. 1) needs to be analyzed for the thermal transfer in the tissue. For the thermal boundary condition, the heat flux is assumed to approach zero at the outer boundaries of the brain tissue [17]. The initial condition is a steady-state temperature uniform distribution at thermo neutral conditions $(T(x, r, 0) = 38.5^{\circ}\mathrm{C})$. The typical values for tissue and air properties for numerical calculation are presented in Table 2 [18] and [19].

B. ANIMAL PREPARATION AND EXPERIMENTAL PROCEDURE

Experiments were conducted on nine piglets (five females and four males), with an average age of 4.5 ± 1.5 days old and an average weight of 3.7kg ± 1.2kg. All animal experiments were approved by the Animal Use Subcommittee of the Canadian Council on Animal Care at the University of Western Ontario. Newborn Duroc cross piglets were obtained from a local supplier on the morning of the experiment. Piglets were anesthetized with 1-2% isoflurane (3-4% during preparatory surgery). A tracheotomy was performed and the piglet was ventilated with a volume-controlled mechanical ventilator to deliver a mixture of oxygen and medical air (2:1). A femoral artery was catheterized to monitor heart rate (HR) and mean arterial blood pressure (MAP) and to intermittently collect arterial blood samples for gas (p_aCO_2, p_aO_2), pH and glucose analysis. Arterial CO_2 tension (p_aCO_2) was monitored throughout the experiment, either directly by blood gas measurements or by the end-tidal CO_2 tension, and maintained at normocapnia between 37-42 mmHg by adjusting the breathing rate and volume. Arterial oxygen tension (p_aO_2) was maintained at a level between 90-130 mmHg by adjusting the ratio of O_2 to medical air. Blood glucose was monitored intermittently and if it fell below 4.5 mmol/L, a 1-2 ml infusion of 25% glucose solution was administered intravenously. After surgery, piglets were maintained on 1-2% isoflurane at normothermia using a heated water blanket to maintain rectal temperature between 38-39°C. Piglets were randomized in two groups, a control group in which piglets were just covered with blankets to maintain their body temperature (Group I, $n = 4$); and a pulmonary cooling group (Group II, $n = 5$). Heat loss through respiratory airways occurs by cooling of inhalation gases ($\mathrm{T_{in}} \approx -3^{\circ}\mathrm{C} \pm 3^{\circ}\mathrm{C}$) immediately before entering the trachea via a shortened endotracheal tube. The body of each piglet was fully covered by blankets for the duration of each experiment. Flow rate of cold air to the lung was ~1.5 L/min. (i.e., tidal volume of 30 ml and average respiratory rate of 50 breaths per minutes). Rectal temperature was recorded from a rectal probe (VWR rectal digital thermometer with 0.1°C precision, VWR International Inc) inserted to a depth of 3-4 cm from the anal margin. Deep brain temperature was also measured continuously with a thermocouple probe (OxyLab pO_2 with 0.2°C accuracy and 0.1°C resolution over range of 20-50°C; Oxford Optronix, Ltd., Oxford, UK). A burr hole 1.5 cm posterior to the bregma along the mid-line was made in the skull. The needle thermocouple probe was inserted through the burr hole into the brain to a depth of 2 cm from the brain surface to measure brain temperature. Each experiment was completed within 5 hours.

TABLE 2. Base set of parameters used in heat sink thermal model.

Symbol	Unit	Value
$\rho_{B,m}$	$(\mathrm{kg.m^{-3}})$	1030
C_b	$(\mathrm{J.kg^{-1}.^oC^{-1}})$	3643
Q_m	$(\mathrm{W.m^{-3}})$	420
Q_B	$(\mathrm{W.m^{-3}})$	5370
M_m	$(\mathrm{kg.s^{-1}.m^{-2}.Pa^{-1}})$	$1.3\mathrm{x}10^{-6}$
h_{bt}	$(\mathrm{W.m^{-2}.^oC^{-1}})$	10000
h′	$(\mathrm{W.m^{-2}.^oC^{-1}})$	50
H	$(\mathrm{J.kg^{-1}})$	2431
a	(m)	0.005
b	(m)	0.025
L	(m)	0.3
u	$(\mathrm{m.s^{-1}})$	0.68
T_{in}	(°C)	5
k	$(\mathrm{W.m^{-1}.^oC^{-1}})$	0.5
A	$(\mathrm{m^2})$	$7.85\mathrm{x}10^{-5}$
S	(m)	0.032
ω_b	$(\mathrm{kg.m^{-3}.s^{-1}})$, $(\mathrm{ml.100g^{-1}.min^{-1}})$	3-11,(15-66)
c_1, c_2, c_3, c_4, c_5, c_6		-5800, 1.4, -0.05, $4.2\mathrm{x}10^{-5}$, $7.8\mathrm{x}10^{-5}$, 6.5
φ		0.3

After the last measurement, the animals were sacrificed using potassium chloride IV (1-2 ml/kg, 2 mEq/mL) while on 5% inhaled isoflurane. The ambient temperature of the animal laboratory was maintained relatively constant at ∼22°C.

C. PULMONARY COOLING APPROACH

Cold inspired air was generated by circulating inhalation air, delivered from a mechanical ventilator through a coiled heat exchanger immersed completely in a cooling bath filled with cryogenic cooling liquid (Ethylene glycol, VWR International Inc) before being delivered to the piglet, as shown in Figure 2. Before starting the cooling process, the cooling unit (Polyscience refrigerated/heated circulating bath with performance digital temperature controller, model PD07R-40, Polyscience International Inc, Illinois, USA) which controls the temperature of the cooling bath, was set to −20°C with a temperature stability of ±0.05°C over 30-45 min; settings were kept the same during the entire experiment. The inhaled temperature (≈−3°C ± 3°C) was monitored between the air cooling system and endotracheal tube. During expiration, air leaving the lungs at body temperature is cooled as it passes along the respiratory tract by mixing with cold inspired air.

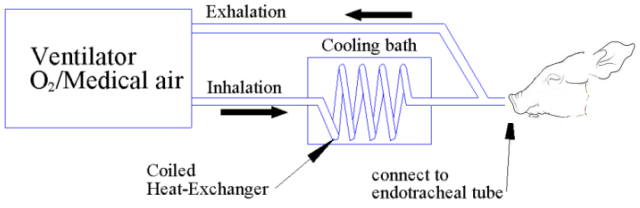

FIGURE 2. Schematic representation of the cooling circuit used for pulmonary cooling. The 7-litre container was filled with a cryogenic cooling liquid (Ethylene glycol).

D. STATISTICAL ANALYSIS

SPSS 17.0.0 (SPSS, Inc, Chicago, IL) was used for all statistical analyses. Normality of the distribution of the measurements was verified using Kolmogorov–Smirnov (KS) test. Comparisons between time-based measurements within groups were performed by Friedman test. Man Whitney U test was used to determine statistical differences of cooling rates as a function of treatment group. Statistical significance was based on $p-$value < 0.05. All data are presented as mean ± standard deviation (SD) unless otherwise noted.

III. RESULTS

Table 3 displays a summary of the measured physiological parameters of the piglets (MAP, HR, p_aO_2 and p_aCO_2) in the groups I and II. The HR and MAP dropped slowly through the pulmonary cooling approach from 152 ± 38 and 55 ± 10 to 141 ± 31 and 47 ± 7, respectively. No significant changes were found between the two groups with respect to HR, MAP, p_aO_2, p_aCO_2, tHb, or pH.

Figure 3(a) displays the average cooling rates as monitored in the brain obtained from groups I and II as well as

TABLE 3. Physiological parameters measured at different groups. Values are mean ± SD.

Variable		*Baseline* *1-60min*	*Cooling* *0.5hr*	*1.5hr*	*3hr*
MAP (mmHg)	*Group I*	*55±7*	*52±6*	*54±7*	*53±5*
	Group II	*55±10*	*56±10*	*52±7*	*47±7*
HR (bpm)	*Group I*	*162±16*	*163±15*	*162±16*	*157±18*
	Group II	*152±38*	*156±51*	*155±40*	*141±31*
p_aCO_2 (mmHg)	*Group I*	*39±3*	*40±3*	*39±3*	*39±2*
	Group II	*42±3*	*41±2*	*37±2*	*41±2*
p_aO_2 (mmHg)	*Group I*	*131±44*	*133±32*	*125±30*	*142±24*
	Group II	*127±40*	*132±35*	*128±30*	*127±34*

theoretical models for O_2-medical air (1:2) and O_2-Xe (1:2) conditions. In animal experiments, the mean brain cooling rate was significantly greater ($p < 0.05$) in the pulmonary group (i.e., Group II) as compared to the control group (Group I). Figure 3-(b) displays the measurements of the brain temperature as a function of time during ventilation of cold O_2-medical air (1:2) in both experimental and theoretical models. Temperatures were recorded manually at 5-minute intervals throughout the experiments; however, for clarity the data are shown at 15-minute intervals. In the animal experiments, following the cooling process the brain temperature fell from a baseline of 38.3°C ± 0.3°C to 36.5°C ±

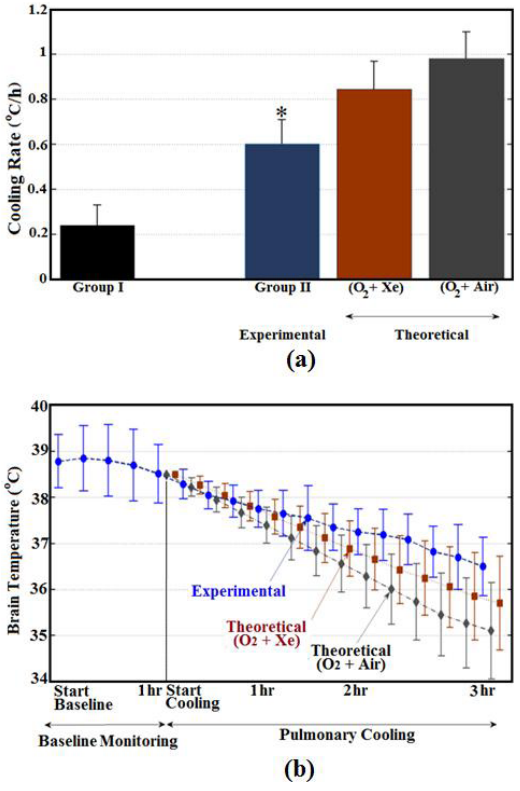

FIGURE 3. (a) Median cooling rate for brain as a function of groups and theoretical predictions; (b) Brain temperature measurements over time for experimental and theoretical model. ∗ signifies a statistically significant difference between pulmonary cooling group versus control group ($p < 0.05$). Values are shown as mean ± SD.

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0.6°C, which corresponded to a mean cooling rate of 0.6°C/h ± 0.1°C/h. Numerical simulations for two different air conditions (i.e., O_2-medical air and O_2-Xe) during pulmonary cooling show that brain temperature dropped to 35.1°C ± 0.4°C and 35.7°C ± 0.5°C which corresponded to a mean cooling rate of 1.1°C/h ± 0.3°C/h and 0.8°C/h ± 0.3°C/h, respectively [Figure 3-(a)]. Average temperature difference between the two air streams was 0.2°C ± 0.1°C over the three hour simulation. Numerical simulations show no significant differences between the two different inhaled gas mixtures with respect to rates of cooling. Furthermore, there was no difference between numerical simulation and experimental data for the O_2-medical air numerical simulation versus O_2-medical experimental group.

Three hours after commencement of cooling, both brain and rectal temperature decreased from 38.6°C ± 0.6°C and 38.2°C ± 0.8°C to 35.9°C ± 0.9°C and 35.3°C ± 0.9°C which corresponded to mean cooling rates of 0.6°C/h ± 0.1°C/h and 0.6°C/h ± 0.2°C/h, respectively as displayed in Figure 4. During the baseline monitoring period, brain and rectal temperature variations were the same (brain and rectal: 0.3°C ± 0.1°C). Average temperature difference between rectum and brain was 0.5°C ± 0.1°C during all animal experiments. Temperature gradient within the piglet's brain, calculated as the difference between frontal and parietal lobes, was not more than 0.1°C in all experiments.

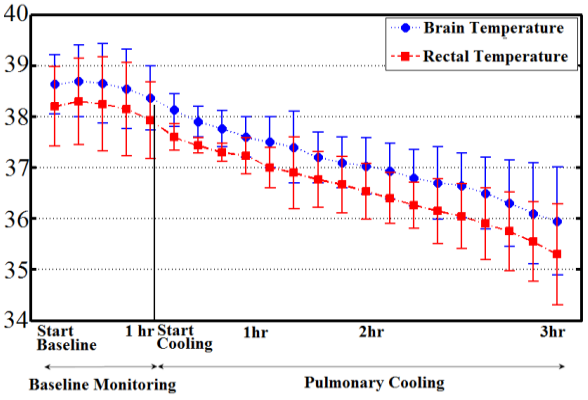

FIGURE 4. Brain and rectal temperature over time for pulmonary cooling method. Values are shown as mean ± SD.

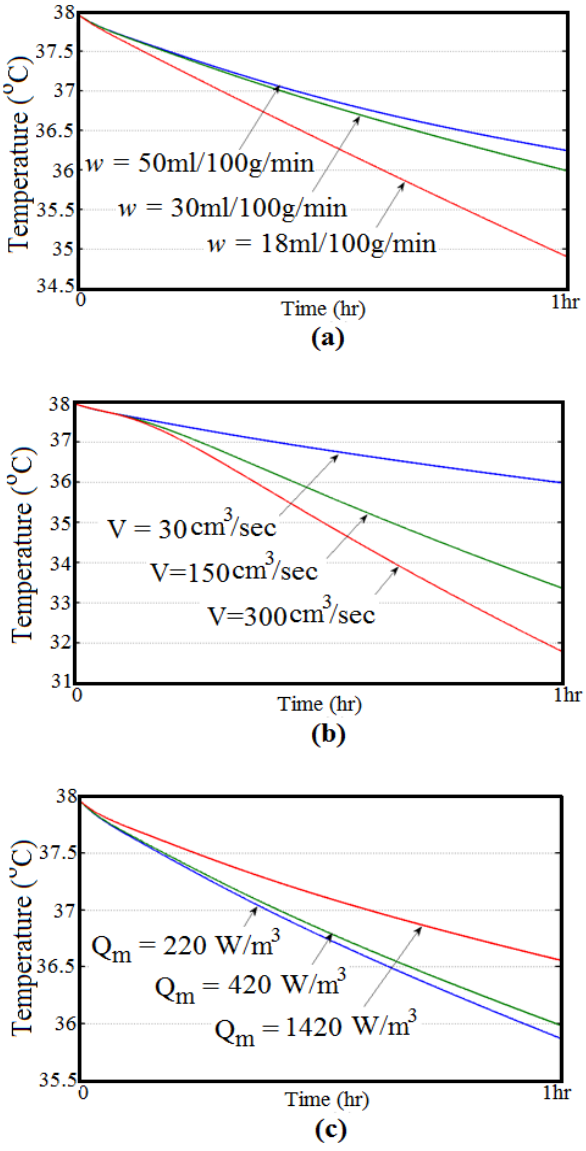

FIGURE 5. Effects of (a) blood perfusion level; (b) local mean longitudinal air velocity, and (c) metabolic rate of tissues on blood temperature response across respiratory tract. Calculation were carried out with thermal conductivity $k = 0.5\ \mathrm{W{\cdot}m^{-1}{\cdot}{^\circ}C^{-1}}$, flowing air temperature $T_{in} = 5°C$, metabolic rate $Q_m = 420\ \mathrm{W{\cdot}m^{-3}}$, local mean longitudinal air velocity $V = 30\ \mathrm{cm^3{\cdot}s^{-1}}$ and blood perfusion rate $\omega_b = 50\ \mathrm{ml{\cdot}min^{-1}{\cdot}100g^{-1}}$ as default values for each simulation.

In addition, numerical calculations were performed to investigate the effect of some physiological parameters such as blood perfusion, metabolic rate and local mean longitudinal air velocity across the respiratory tract as displayed in Figure 5(a-c). Figure 5(a) shows the temperature change for three different blood perfusion rates. It can be seen that higher blood perfusion tends to prevent the biological tissues from cooling. As Figure 5(b) displays, higher air velocity yields greater cooling effects (as one would expect as convective heat transfer increases). Figure 5(c) also shows the temperature responses with different metabolic rates. Clearly, the cooling rate can be increased with lower metabolic rate. For simplicity, all tests investigating the effect of different parameters on temperature profiles have been carried out for one hour.

IV. DISCUSION

Since the entire cardiac output passes through the pulmonary capillary network and the heat of the body can be transferred to the environment via the vast alveolar surface, the lung can serve as a core heat exchanger. As a consequence of conduction, convection, and water evaporation, heat is lost from the trachea and respiratory tract, and the temperature of

these surfaces falls below body temperature and this eventually cooled down the whole body. Based on this heat exchange method, we showed that pulmonary cooling can be achieved by cooling of inhalation gases via shortened endotracheal tube: the brain and rectal temperature in piglets dropped from 38.6°C ± 0.6°C and 38.2°C ± 0.8°C to 35.9°C ± 0.9°C and 35.3°C ± 0.9°C in three hours which corresponded to a mean brain cooling rate of 0.6°C/h ± 0.1°C/h and 0.6°C/h ± 0.2°C/h, respectively. The decline in rectal temperature following the brain temperature may be due to the balance between heat production in the rest of the body and heat lost across the respiratory tract. The low cooling rate achieved in this study could be explained by a combination of different reasons. Employing a single endotracheal tube for both inspiratory and expiratory gas increases the efficiency of the heating as cold air is warmed rapidly by countercurrent heat exchange between inspired and expired gas in the endotracheal tube and upper airways before reaching the alveoli. The heat exchange in the upper airway is a powerful mechanism for thermal insulation of alveolar gas and normally prevents penetration of cold environmental gas beyond 10-15cm [20]. Similarly, Shaffer *et al.* [21] and Forman *et al.* [9] demonstrated the method of pulmonary cooling with liquid ventilation (perfluorocarbon (PFC) liquids at 20°C-30°C) to induce hypothermia. The problem with their method is associated with the safety profile of its coolant. PFCs are powerful greenhouse gases and deplete the ozone layer and are listed as toxic substances under the Canadian Environmental Protection Act (CEPA) [22]. Another safety concern is the risk of coolant aspiration which might cause lung damage over prolonged periods since neural protection therapy may involve mild hypothermia being maintained for a period of 72 hours [23].

The effect of different thermal properties of respiratory gas on brain cooling was examined by two different air streams using a control-volume explicit finite-difference method. Although the thermal conductivity and specific heat capacity of air are 5-6 times more than Xe, the predicted cooling effect across the respiratory tract and within the brain was still very small for both gas mixtures, O_2-medical air (1:2) and O_2-Xe (1:2). There are several limitations in our numerical study that should be pointed out. For example, more complex geometrical and physiological parameters of the respiratory system may be incorporated for a more comprehensive estimation of brain tissue temperature during pulmonary cooling. Furthermore, some brain and respiratory thermal parameters, including air velocity and the metabolic rate, are assumed to be constant in the tissue due to the relatively small change in temperature. However, it has been shown that reducing brain tissue temperature from 37°C to 34°C reduces the metabolic rate by about 25%.

Piglets were studied because they are considered close to newborn humans in terms of anatomy, physiology and biochemistry [24]. Similarities of the piglet to the newborn human in brain size, metabolism [25], circulation [26], and response to hypoxic-ischemic [27] stresses make the newborn piglet a suitable model to develop and test the applicability of pulmonary cooling for clinical treatment of hypoxic-ischemic encephalopathy. The anatomy of the airway system in the piglets permits inhalation studies and functional respiratory studies. Rogers *et al.* point out the many similarities between human and pig lungs of relevance to anatomy, histology, and immune and inflammatory responses [28]. Moreover, thermoregulatory responses in newborn piglets were progressively achieved within 2 days of birth [29] and the weight of the piglets in this study (3.7 ± 1.2kg) was closer to that of neonates when compared to other species. A limitation of this study is that the brain temperature was measured only at one position and, therefore, no information was obtained about homogeneity of regional brain temperature. However, two preliminary experiments had examined the temperature gradient within a piglet's brain, calculated as the difference between frontal and parietal lobes by inserting one probe in each region, and this was found to be no more than 0.1°C.

We demonstrated that cooling via the lungs could slowly reduce the brain and rectal temperatures of newborn piglets; however, there may be limitations in transferring this to neonatal practice as the current cooling methods to induce mild therapeutic hypothermia may be convenient to use and more effective [23], [30]. Moreover, there are many types of breathing disorders related to lung development which occur most often when the lungs of premature newborns may not have time to fully develop. Pulmonary cooling may not be used for such newborns, as they are likely to have had limited pulmonary function and respiratory distress. However, unlike newborn piglets, in adult pigs this technique might be more beneficial due to the larger tidal volume which may perhaps maximize the cooling effect. Hence, more experimental studies are necessary to evaluate the efficiency of the device and reproducibility of the results in large animal models.

Different cooling methods have different physiological and biochemical effects. Even for the same method, the cooling effect and clinical outcome could be totally different due to the imposed initiate time, cooling duration, cooling depth, and rewarming rate. The general agreements among clinicians are early cooling initiation within the treatment window after injury, and gradual rewarming (i.e., 0.1°C/h-0.4°C/h). Developing a selective brain cooling (SBC) approach, which induces rapid cooling and can be initiated early, would yield maximum neuroprotection and minimize adverse effects associated with whole body cooling. However, SBC ideally requires a non-invasive method that can measure deep brain temperature, since core measurements may not reflect brain temperature. Therefore, improved cooling and monitoring technologies are still very desirable to maximize the full potential of this therapy. Based on anatomical features, cooling the nasopharynx may offer the capability to cool the brain selectively due to anatomic proximity to the internal carotid arteries, cerebrospinal fluid and cavernous sinus. However, in humans, it was argued that the face and the

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surface of nasal mucosa as sources of cool venous blood are small in relation to the mass of the brain and the carotid rete, where heat exchange might occur, does not exist [31]. Because humans do not have a carotid rete, some have suggested that there is no counter-current heat exchange in the cavernous sinus and, as a result, human selective brain cooling is not possible. Yet the rete is not a prerequisite for cooling the brain because several other mammals without a carotid rete clearly demonstrate SBC [32], [33].

V. CONCLUSION

In conclusion, we demonstrated that pulmonary cooling by cooling of inhalation gases via shortened endotracheal tube can slowly reduce brain and core body temperature of newborn piglets. In order to avoid the complications associated with pulmonary cooling and systemic hypothermia, as the next step, we will be investigating the feasibility and efficiency of nasopharyngeal selective brain cooling by continuously blowing cold air into the nostrils at different flow rates in newborn piglets. Furthermore, we investigated the effects of the individual's physiological and environmental variables (such as blood perfusion, metabolic rate, and air velocity). According to the numerical results, decreasing the metabolic rate and increasing air velocity is helpful to maximize the cooling effect. Numerical simulations show no significant differences between two different inhaled conditions, i.e., O_2-medical air (1:2) and O_2-Xe (1:2) with respect to cooling rate. Furthermore, there was no significant difference between the numerical data using an air mixture of O_2-medical air and experimental data. Although Xe is attractive for combination therapy with HT due to its lack of chemical activity and side effects, the results in this study indicated that using O_2-Xe (1:2) in pulmonary cooling was less effective compared with O_2-medical air (1:2), due to its having a lower heat capacity than air.

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NOMENCLATURE

T	Temperature
ρ	Density
c	Specific heat capacity
k	Thermal conductivity
ω	Volumetric perfusion rate
Q	Energy generatation associated with production of heat due to the cellular metabolism
h	Heat convection coefficients between mucosal and flowing air
h'	Heat convection coefficients between tissue and flowing air
h_{bt}	Heat convection coefficients between tissue and blood
H	Latent heat of vaporization
M	Water penetrative coefficient
ϕ	Relative humidity of flowing air
a	Radius of respiratory tract
b	External radius of calculation domain
L	Longitudinal length of human respiratory tract
$p*$	Saturated vapor pressure
S	Local airway cross section
P	Air perimeter
x	Longitudinal distance
r	Transverse distance
t	Time

SUBSCRIPTS

A	Air condition (i.e., O_2-Air, O_2-Xe)
b	Blood condition
in	Inhalation
m	Mucous tissue
B	Brain
Xe	Xenon

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