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Numerical Simulation of Scalp Cooling to Prevent Chemotherapy–Induced Alopecia.

Francis-Paul E.M. Janssen*, Gerard M.J. van Leeuwen, Anton A. van Steenhoven.

[1]*Department of Biomedical Engineering, Eindhoven University of Technology, PO Box 513, Eindhoven, The Netherlands,* f.e.m.janssen@tue.nl.*

Abstract

One way of treating cancer is by chemotherapy. Side–effects of chemotherapy include hair loss. Cooling the scalp during treatment can reduce hair loss. For this cooling, a cap containing a cold fluid (cold cap) is used. However, the rate of success of this method varies strongly, because precise mechanisms of preservation are unknown.

Temperature and perfusion are thought to play an important role in the hair preservative effect of scalp cooling. To gain more insight into these parameters, a computer model has been developed. With this, the influence of perfusion models is studied.

The computer model comprises a head and cold cap, modeled with concentric shells representing brain, skull, fat, skin, hair and cold cap. Metabolism is temperature dependent and two relations from literature are used to model temperature dependent perfusion. Pennes' bio–heat equation is used to determine the heat transfer in the head. Steady state temperatures without cold cap are calculated and used as basal temperatures for metabolism and perfusion. Then, a cold cap (T = -30˚C) is added and the development of temperature in time is calculated. For constant perfusion, a minimum skin temperature of 16.0˚C is reached after 476 seconds. When skin blood flow is set to zero, the minimum temperature drops a further 1.5˚C to 14.5˚C. For the perfusion models, the drop in skin temperature results in a decreased perfusion, down to a value ranging from 19% to 33% of base level.

The thickness of the hair layer is of great importance for both perfusion and temperature. Reducing the thickness resulted in a decrease in temperature of 5.7˚C, and decreased relative perfusion by a further 0.10, indicating that chances of preserving hair are higher. For optimal protection against hair loss, the cold cap should fit the scalp as tightly as possible.

Introduction

Cancer is a common illness. Each year, 0.5% of the US population is newly diagnosed with cancer [8]. One way of treating cancer is by chemotherapy. It kills rapidly dividing cells, and usually it is relatively specific for cancer cells. However, other constantly dividing cells are also affected, such as the matrix cells in the hair follicle that produce the hair shaft.

Administration of chemotherapy induces toxicity in these matrix cells. The root sheaths may become necrotic, or, in less severe cases, form a weak, constricted hair shaft that then easily breaks [10]. The resulting hair loss is rapid and extensive, since more than 90% of scalp follicles are in a growing phase at any given time [5].

Although temporarily, hair loss is one of the most feared side effects of cancer therapy [4]. It causes psychological stress, which may even lead some patients to reject potentially curative treatment [9]. It has been shown that scalp cooling during the administration of the cytotoxic drugs can reduce hair loss (e.g., [12]). For this, a cap containing a cold fluid (cold cap) is placed.

The current hypothesis for the mechanism is that by cooling the scalp skin, blood perfusion is reduced. This reduces the total amount of cytotoxic drugs that are available for uptake in the matrix cells. In addition, reaction rates decrease with lower temperature, reducing chemotherapy uptake. The combined effect gives a drastic reduction in cell damage, such that hairs are preserved.

However, the effect of scalp cooling varies strongly [9]. One of the reasons for the varying success of scalp cooling is that current day treatment is based on trial and error [3]. A systematic evaluation of the current hypothesis is necessary for a better understanding of the various important parameters of scalp cooling. To gain

Nomenclature

c	Specific heat	J/kg K	**Greek**		
Cs	Vasoconstriction	-	α	Proportional model constant	-
h	Heat transfer coefficient	W/m^2 K	ε	Emissivity	-
k	Thermal conductivity	W/m K	ω	Blood perfusion rate	kg/m^3 s
M	Metabolic rate	W/m^3	ρ	Density	kg/m^3
T	Temperature	K			
t	Time	s	**Subscript**		
q''	Heat flux	W/m^2	0	Basal	
			sk	Skin	

more insight into the effect of cooling, a computer model has been developed to study the mutual influence of temperature on perfusion during cooling with a cold cap, using different perfusion models. With temperature–perfusion relations from the literature, estimates can be found for the decrease in local drug delivery.

Methods

The heat produced by metabolic processes in the human body is transported by means of conduction and convection. These heat transport mechanisms occurring in the living tissue were modeled by Pennes [11] in the well–known "bio–heat transfer" equation:

$$\rho c \frac{\partial T}{\partial t} = \nabla(k \nabla T) + (c\omega)_{\text{blood}}\left(T_{\text{artery}} - T\right) + \text{M} \qquad (1)$$

in which ρ, c and k are the density, specific heat and conductivity, respectively. T is the local tissue temperature and T_{artery} the temperature of the blood, in this study assumed to be constant and set to 37°C. ω and M are the blood perfusion rate and the metabolic heat production in the tissue, respectively.

The Pennes' model uses a "heat–sink" approach to model perfusion. It assumes that all heat transfer takes place in the capillaries in the tissue. Although this assumption has been debated for its validity [1], it has been shown that this equation produces accurate results for the temperature distribution in the head during scalp cooling [14].

During scalp cooling, a large drop in skin temperature occurs. This influences both metabolism and perfusion.

Metabolic heat production is modeled according to the so–called Q10–effect [13]. It states that a temperature drop of ten degrees Celsius results in a 50% decrease in heat production:

$$\text{M} = \text{M}_0 \cdot 2^{(T-T_0)/10} \qquad (2)$$

Local skin blood flow is also affected by this reduction in metabolic heat production [7].

In addition, the decrease in temperature may trigger changes in blood flow by thermoregulation. To see the influence of these two mechanisms, three different perfusion models are used.

Perfusion models

The first model (constant model) uses a constant α ($0 < \alpha < 1$), to obtain a constant perfusion, proportional to basal perfusion:

$$\omega_{\text{sk}} = \alpha \cdot \omega_{\text{sk},0} \qquad (3)$$

The second model (Stolwijk model) uses the reduced perfusion corresponding to the decrease in metabolic heat production (Q10–effect):

$$\omega_{\text{sk}} = \omega_{\text{sk},0} \cdot 2^{\left(T_{sk} - T_{\text{sk},0}\right)/10} \qquad (4)$$

In this equation, T_0 is the local neutral temperature, obtained from steady state calculations.

Finally, the third model (Fiala model) incorporates the Q10–effect and an extra term to represent vasoconstriction (Cs):

$$\omega_{\text{sk}} = \frac{\omega_{\text{sk},0}}{1 + \text{Cs}} \cdot 2^{\left(T_{sk} - T_{\text{sk},0}\right)/10} \qquad (5)$$

Fiala [7] used the Cs term to describe the reaction of local skin blood flow to variations in mean skin temperature of the whole body. For this study, an adapted equation for Cs is used, since only scalp skin temperature is affected:

$$\text{Cs} = 2.92\left[\tanh\left(0.0284\Delta T_{\text{sk}} + 1.07\right) - 1\right]\Delta T_{\text{sk}} + 0.326\Delta T_{\text{sk}} \frac{\text{d}T_{\text{sk}}}{\text{d}t} \qquad (6)$$

with ΔT_{sk} defined as:

$$\Delta T_{\text{sk}} = T_{sk} - T_{sk,0} \qquad (7)$$

Table I: Parameters of the numerical model [15].

	Outer radius r [mm]	Conductivity k [W/m K]	Specific Heat c [J/kg K]	Density ρ [kg/m^3]	Metabolic Rate M [W/m^3]	Blood Flow ω [kg/m^3 s]
Brain	90.0	0.536	3643	1030	5370	5.37
Skull	96.5	0.650	1590	1520	0.0	0.06
Fat	97.5	0.217	2367	888	300	0.31
Skin (inner)	98.5	0.342	3662	1070	1800	1.8
Skin (outer)	99.5	0.342	3662	1070	0.0	0.0
Hair	100.5	0.026	1000	1.0	0.0	0.0
Cold Cap	110.5	0.500	4300	1000	0.0	0.0

Numerical Methods

The computer model consists of a typical head and a cold cap, both idealized with spherical elements representing brain, skull, fat, skin, hair and cold cap. The model is essentially one dimensional, which means that only radial conduction will be accounted for. Tissue layers are assumed to have homogeneous properties. Dimensions, thermal properties, basal blood flow and basal metabolic rate of each layer are taken from literature [15] and are shown in Table I.

Boundary conditions for head and cold cap include convective heat transfer and radiative heat transfer. Convective heat transfer from head or cold cap to the surroundings is modeled as

$$q'' = h\left(T - T_{\text{ambient}}\right) \tag{8}$$

in which h is the heat transfer coefficient. Its value was taken from literature as 4 W / K m^2 [15]. The thermo–neutral temperature distribution (i.e. no response of thermoregulation), was calculated with the ambient temperature (T_{ambient}) set to 20˚C.

Radiative heat transfer from the cap surface to the surroundings and between head and cold cap is modeled as

$$q'' = \sigma\varepsilon\left(T_1^4 - T_2^4\right) \tag{9}$$

in which σ is the Stefan Boltzmann constant (σ = $5.669 \cdot 10^{-8}$ W / m^2 K^4) and ε the emissivity. Emmisivity of both head and cold cap was taken as 1.0.

For cooling of a homogeneous sphere with constant material properties, temperature profiles in the sphere at various times during cooling matched the analytical solutions to within 0.06˚C [2]. Steady state temperatures of the model with heat generation and perfusion were also compared to the analytical solution [7] and the results are accurate to within $5 \cdot 10^{-3}$˚C.

Simulation of a scalp cooling procedure consisted of two steps. First, the temperature without a cold cap was calculated, keeping metabolism and perfusion constant. The resulting temperature profile was used as basal temperature profile for temperature dependent metabolism and skin blood flow. Then, a cold cap is added to the model. In practice, a cold cap can either be continuously cooled, or only be cooled before application. The first cold cap has an initial temperature of -5˚C and uses a cooling system that circulates fluid (temperature -5˚C) at 10 liters per minute (ω_{sk} = 119 kg/m^3 s). The second cold cap does not circulate fluid and has an initial temperature of -30˚C.

In a parameter study the influence of varying skin perfusion rates and different perfusion models on the temperature response was studied.

Results

Perfusion Models

First, the temperature development in time for different perfusion models was calculated for the pre–cooled cap. To indicate the boundaries of response, i.e. the minimum and maximum temperature responses, the constant model was used. For the constant model with α = 1, the scalp temperature dropped from 34.3˚C and reached a minimum of 16.0˚C after 476 seconds (Fig. 1A), after which it gradually returned to a normal value. With α = 0, minimum temperature was 14.5˚C, which was reached after 535 seconds.

Next, the Stolwijk and Fiala models were used (Eq. 4 and 5, respectively). The difference in minimum temperature between the Stolwijk model and the Fiala model was 0.2˚C (15.1˚C versus 14.9˚C, respectively). For the Stolwijk model, perfusion was reduced down to a relative value of 0.33 (Fig. 1B). After a strong decrease in the beginning of the simulation, the Fiala model shows a minimum relative value of 0.19.

Size of Hair Layer

In a parameter study, Van Lenthe [15] showed that the thickness of the hair layer is the most critical parameter in lowering the scalp temperature. To see the influence of this parameter on relative perfusion and scalp temperature, simulations were done using the cold cap with cooling system (T = -5˚C), to obtain stationary situations. The standard model uses a hair layer of 1mm, and resulted in a skin temperature of 17.2˚C. Doubling the hair layer thickness increases relative perfusion in the Stolwijk model from 0.37 to 0.49 (Fig. 2). For the Fiala model, the perfusion in the cooled state changes from 0.23 to 0.35. In addition, the minimum temperature of the

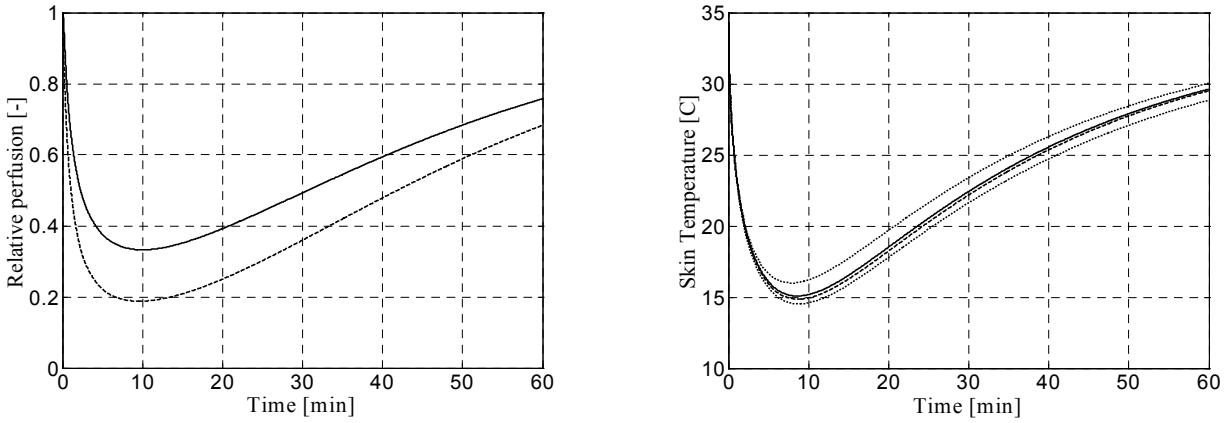

Figure 1: A: Development of the skin blood flow for the Stolwijk model (solid line) and the Fiala model (dashed line).
B: Development of the skin temperature for different perfusion models. Upper and lower dotted line are of the proportional model with α = 1 and α = 0, respectively. The solid line represents the Stolwijk model, and the dashed line the Fiala model.

skin is increased by 5.2˚C with respect to the standard model.

A hair layer of 0.5mm resulted in a minimum skin temperature that is 5.7˚C lower than that of the standard model. This temperature reduction decreases the perfusion from a relative value of 0.37 down to 0.27 for the Stolwijk model. The Fiala model showed a perfusion reduction from 0.23 down to 0.14.

Conclusions and Discussion

The perfusion models show a reduction in skin blood flow during cooling. For the Stolwijk model, this reduction is 67%. In the Fiala model, vasoconstriction is also modeled, resulting in a skin blood flow reduction of 81%.

The hair layer has a significant effect on both temperature and perfusion. An increase in hair layer from 1mm to 2mm results in an increase in minimum skin temperature of 5.4˚C. Relative perfusion increases from 0.37 to 0.49 (Stolwijk model). For the Fiala model, relative perfusion increases from 0.23 to 0.35. Decreasing the thickness of the hair layer resulted in a further decrease in relative perfusion. The Stolwijk model shows a decrease to 0.27 and in the Fiala model, perfusion is reduced to 0.14. To maximize the hair preserving potential, the cold cap should have a tight fit, to reduce temperature and perfusion as much as possible.

Decorti [6] showed that temperature is a very important determinant for uptake of doxorubicin (a type of chemotherapy–drugs). They performed experiments with healthy kidney epithelial cells, showing that drug uptake was considerably reduced when temperature was lowered from 37˚C to 4˚C (Fig. 3A). In addition, they studied the relationship between drug concentration and the initial doxorubicin uptake (15 min). At 4˚C, this relationship was linear. At 37˚C, uptake of doxorubicin was greater and showed a trend for saturation (Fig. 3B).

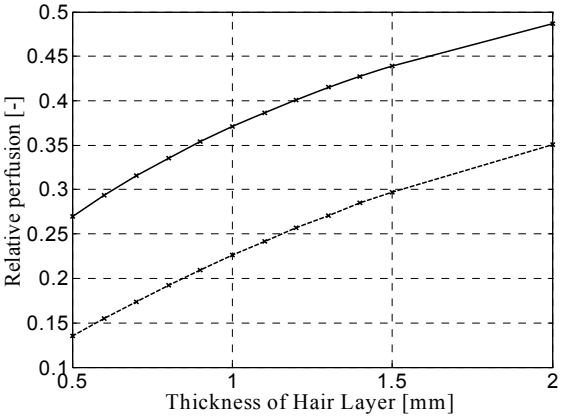

Figure 2: Influence of the thickness of the hair layer on relative perfusion. The solid line represents the Stolwijk model, the dashed line the Fiala model.

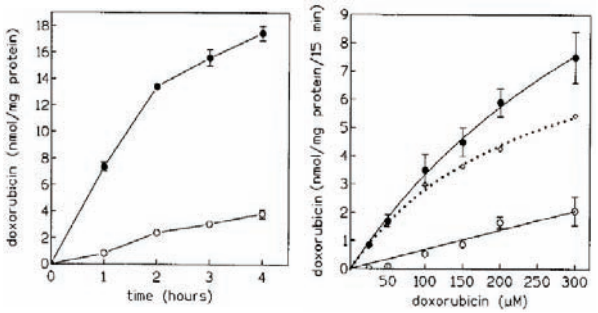

Figure 3: A. Effect of temperature on doxorubicin uptake at 37˚C (●) or 4˚C (○) [6].
B. Concentration dependence of doxorubicin uptake (15 min) at 37˚C (●) or 4˚C (○). The dotted line indicates the difference of doxorubicin uptake at 37˚C and 4˚C [6].

Although results from this study may not be generalized to other cell types, the above study indicates that reducing temperature during scalp cooling with 20˚C decreases the uptake of chemotherapy. In addition, the resulting decrease in perfusion of 60% to 80% leads to a diminished delivery of drugs to the hair follicle cell, lowering drug uptake. In total, the amount of damage done to the matrix cells will be lower, increasing the chances of preserving hair.

To understand the precise effect of reduced perfusion and temperature on cell death on a local level, studies are needed on drug uptake and cell death at different temperatures. In the future, these processes will be quantified by experiments on single hairs and by numerical modeling. Furthermore, the relationship between temperature reduction and perfusion will be studied using Laser Doppler Flowmetry.

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