Advanced Course and Workshop on Blood Flow
BF 2005 – (pp.405–414) – Warsaw, 2005.

Biological and Physiological Mechanisms of the Hair Preservative Effect of Scalp Cooling in Chemotherapy-Induced Hair Loss

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Hair loss is a feared side-effect of chemotherapy treatment. It may be prevented by cooling the scalp during administration of cytostatics. The supposed mechanism is that by cooling the scalp, both temperature and perfusion (blood flow) are diminished, affecting drug supply and drug effect in the hair follicle. However, the exact contribution of both temperature and perfusion to the hair preservative effect of scalp cooling is unknown.
Aim of this study is to develop a biological and physiological model of scalp cooling, and to identify the important aspects in scalp cooling. For this, sub models for heat transfer, medicine transport and cell damage are being developed. To tune these models, dedicated experiments are performed on the relationship between temperature and blood flow, and on the influence of temperature and chemotherapy concentration on hair follicle damage.
With the complete model, it will be possible to improve current day scalp cooling treatment.

1. Introduction

When chemotherapy is used as a cancer treatment, partial or complete hair loss does often occur. This causes psychological stress [1], and it is one of the most feared side effects of cancer therapy [2]. By cooling the scalp during chemotherapy treatment this hair loss can be reduced or even prevented [3].

There are two mechanisms that assumedly explain the hair preservative effect of scalp cooling [4]. The first is reduced blood flow to the subcutaneous tissue during cooling, which reduces the amount of drugs being de-

livered to the hair follicle. The other mechanism is a reduced subcutaneous cell metabolism in response to the hypothermia, making hair follicles less susceptible to drug damage.

However, the effect of scalp cooling varies strongly [5] which can partly be attributed to a lack of insight in the precise temperature dependence of these mechanisms. Another important aspect is that it is uncertain whether local variations in skin temperature and blood flow exist during cooling.

In this study, a computer model is being developed to describe all aspects of scalp cooling. The model includes different numerical models to describe drug transport, heat transfer and hair follicle damage and experiments are conducted to improve numerical relations in those models. With the complete model, it will be possible to assess crucial parameters in the design and user protocol of scalp cooling.

2. Experiments on Blood Flow and Temperature

One of the main points of interest in this study is the interplay between temperature and perfusion. In literature, the well known Q_{10} relation of thermal physiology is used to model variations in metabolism (M) and subsequent responses in blood flow (W_B) due to changes in temperature [6, 7]:

$$\begin{aligned} M &= M_0 \cdot Q_{10}^{\frac{(T-T_0)}{10^\circ C}} \\ W_B &= W_{B,0} \cdot Q_{10}^{\frac{(T-T_0)}{10^\circ C}} \end{aligned} \tag{2.1}$$

with values for Q_{10} ranging from 2.0 to 3.0 [6]. However, these values have not been verified for cooling of the human scalp. Even the validity of these functions needs to be assessed.

Therefore, experiments are being performed to investigate the relationship between scalp temperature and scalp blood flow. A laser doppler probe (407, Perimed UK Ltd) and a J-type thermocouple are placed on the scalp skin (frontal skull, slightly off-center to the right). A cold cap system (Paxman Coolers Ltd UK) is used without pre–cooling to cool the skin with a slow rate of approximately 0.1°C/min. Total time of cooling is about 120 minutes.

A result of a preliminary experiment on blood flow and temperature is shown in Figure 1. In this figure, relative perfusion $W_B/W_{B,0}$ is plotted against the temperature difference $\Delta T = T_{\mathrm{sk}} - T_{\mathrm{sk},0}$. Because of the definition of $W_{B,0}$, the graph necessarily includes $\Delta T = 0$, $W_B/W_{B,0} = 1$.

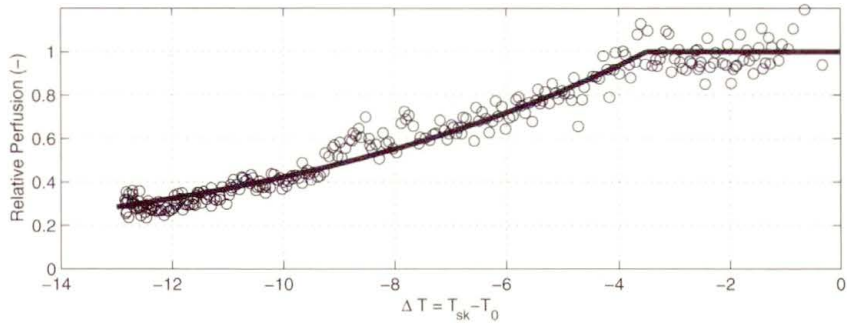

Figure 1. Preliminary experiment on the relationship between temperature and perfusion. Relative perfusion and temperature of the skin are shown during cooling of the skin. The solid line denotes a Q_{10} value of 3.75 with a threshold of 3.5°C.

Perfusion drops down to 28% for a temperature drop of 13°C, which is in agreement with findings of Bülow [4]. Using Eq. (2.1), this would correspond to a Q_{10} value of 2.65.

However, it is striking to see that during the first 3 to 4 degrees of cooling, there is no change in perfusion. This would indicate there is a negative threshold value for changes in blood flow. A fit through the graph yielded a threshold value of 3.5°C, and a Q_{10} value of 3.75.

As stated earlier, these results are from one preliminary experiment. Further experiments are needed to establish the relation and individual variation for the temperature dependence of perfusion.

3. Heat Transfer Model

A numerical model has been made to describe heat transfer in the head during cooling [8]. The head and cold cap are both approximated by spherical elements representing brain, skull, fat, skin, hair and cold cap (Fig. 2). Heat transport in the head is modelled using Pennes' well-known "bio-heat transfer" equation:

$$\rho c \frac{\partial T}{\partial t} = \nabla \cdot (k \nabla T) + W_B (T_A - T) + M$$

in which ρ, c and k are the tissue density, specific heat and thermal conductivity, respectively. T is the local tissue temperature and T_A the temperature of the blood in the main arteries supplying the scalp, here assumed to be

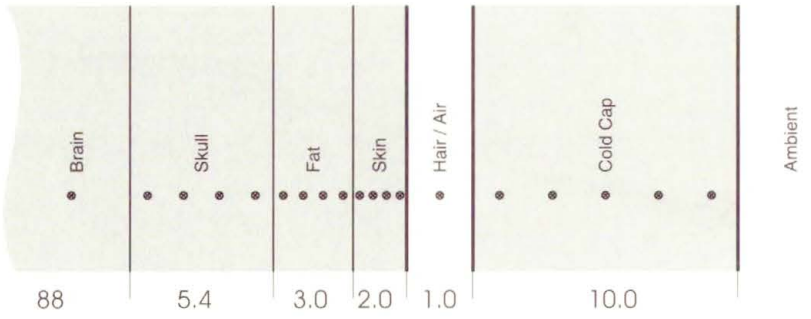

FIGURE 2. Schematic representation of the heat transfer model and placement of the nodes. Dimensions of the model are shown in millimeters.

constant and set to 37°C. Values of these properties used in our standard head model are shown in Table 1.

TABLE 1. Thermophysical tissue parameters used in the standard head mode.

	d [mm]	k [W/(mK)]	Q [W/m^3]	$W_{b,0}$ [kg/(m^{3}s)]
Brain	88.0	0.5	8800	8.5
Skull	5.4	1.0	130	0.15
Fat	3.0	0.2	130	0.2
Skin	2.0	0.384	500	1.5
Hair	2.5	0.026	0	0
Cold Cap	10.0	0.5	0	120

W_B and M are the blood perfusion rate and the metabolic heat production in the tissue, respectively, which are both functions of temperature. Temperature dependent blood flow is modelled using the Q_{10}-thresholdfunction as found in the preliminary experiment:

$$W_B = \begin{cases} W_{b,0} & \text{if } T \geq (T_0 - 3.5); \\ W_{b,0} \cdot 3.75^{\frac{(T-(T_0-3.5))}{10}} & \text{if } T < (T_0 - 3.5). \end{cases} \tag{3.1}$$

At the interface between two different layers, a special numerical method is used to ensure that both temperature and heat flux are continuous across the interface boundaries.

Boundary conditions for the model include convective heat transfer (q''_C) and radiative heat transfer (q''_R) to the surroundings:

$$q''_C = h(T - T_{\text{amb}}),$$
$$q''_R = \sigma(T^4 - T^4_{\text{amb}}).$$

In these equations, h is the heat transfer coefficient appropriate for free convection ($h = 4\,\mathrm{W/(m^2K)}$) and σ is the Stefan Boltzmann constant ($\sigma = 5.669 \times 10^{-8}\,\mathrm{W/(m^2K^4)}$). Ambient temperature ($T_{\mathrm{amb}}$) is set to 20°C.

The cold cap has a thickness of 10 mm and uses a thermal conductivity of 0.5 W/(mK). The coolant in the cap has an estimated mass flow of 0.17 kg/s. This value is adjusted to a flow of $120\,\mathrm{kg/(m^3s)}$, such that it can be used in the Pennes equation. Coolant temperature is set to −8°C.

A parameter study was performed with the heat transfer model. 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 the reference temperature profile (T_0) for temperature dependent metabolism (Eq. 2.1) and blood flow (Eq. 3.1). Then, a cold cap was added to the model and the steady state solution was calculated.

The base model shows a minimum skin temperature of 18.3°C and a relative blood flow of 18%. The results of the parameter study will be compared to the result of the standard model. Results are shown in Table 2.

TABLE 2. Change in minimum skin temperature and relative blood flow during cooling with a cold cap as a result of different parameter values. $\Delta T = T_{\mathrm{min}} - T_{\mathrm{min,standard}}$, so a negative value means a colder skin than in the standard analysis. Blood flow values are given in percentages of blood flow before cooling. Blood flow in the standard analysis was reduced to 18%.

property / scaling factor	×0.5 ΔT [K]	×2.0 ΔT [K]	×0.5 W_B [%]	×2.0 W_B [%]
d_{fat}	3.1	−5	28	9.7
d_{skin}	0.3	−0.2	20	18
d_{hair}	−8.2	3.5	6.4	30
k_{fat}	−3.5	1.5	12	23
k_{hair}	3.4	-2.7	29	13

From this table, it is clear that thickness and thermal conductivity of both the fat layer and the hair layer are the most important parameters that influence skin temperature and perfusion. Changing the hair layer thickness from 1 mm to 2 mm increases temperature by 3.5°C, while changing it from 1 mm to 0.5 mm decreases temperature by 8.2°C. In the first case the perfusion is almost five times the perfusion of the second case.

For the clinic, this means that a good control of the thermal resistance of the hair layer is essential. It should be kept as low as possible to ensure good cooling, without exceeding the limits of thermal comfort for the patient.

4. Physiologically Based Pharmacokinetic Model

To relate drug dosage to toxic effects with the aim to evaluate the effect of scalp cooling, it is first of all necessary to predict the exact concentration of cytotoxic drugs in the hair follicle. For this, Physiologically Based Pharmacokinetic (PBPK) models are useful tools [10]. They divide the body into compartments that represent individual organs and tissue groupings. Physiologic and biochemical constants are used to model transport, clearance and metabolism of drugs with a set of differential equations for the mass balance in each compartment (Fig. 3).

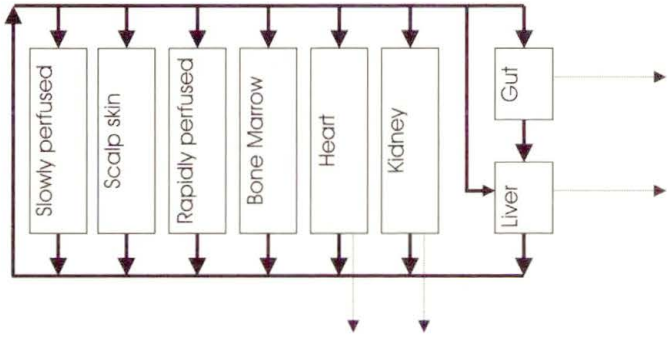

FIGURE 3. Schematic representation of a physiologically based Pharmacokinetic model for DOX. →: blood flow; - -→: metabolic or excretory pathways.

An eight-compartment flow limited model is used [11], incorporating tissue-specific metabolism and biliary and urinary elimination. For each compartment, a generic mass balance equation is used:

$$\frac{dA_i}{dt} = W_{B_i}(C_A - C_{V_i}) - \frac{dA_{E,M_i}}{dt}$$

where A_i is the amount of drug in the compartment in [moles], W_{B_i} is the blood flow through the compartment in [l/s], and C_A and C_{V_i} are the arterial and venous blood concentrations in [moles/m^3]. A_{E,M_i} denotes the amount of drugs that are being excreted or metabolized in the tissue in [moles], showing

either linear kinetics:

$$\frac{dA_{E,M_i}}{dt} = K_{\mathrm{MET}} \cdot C_{V_i} \cdot V_i$$

or saturable chemical–specific binding kinetics (i.e. Michaelis–Menten Kinetics):

$$\frac{dA_{E,M_i}}{dt} = \frac{V_{\mathrm{MAX}} \cdot C_{V_i}}{K_{\mathrm{M}} + C_{V_i}}$$

Here, K_{MET} is a first order metabolic rate constant [s^{-1}], V_i denotes the volume of the i^{th} compartment in [m^3], V_{MAX} is the maximum rate of activity in [moles/s], and K_{M} denotes a Michaelis' constant in [moles/m^3].

The amount of drugs in the blood compartment is calculated using another mass balance.

$$\frac{dA_B}{dt} = \sum_i W_{B_i} C_{V_i} - \sum_i W_{B_i} C_A$$

We use the cytostatic Doxorubicin (DOX) in our model, since it is commonly used, it causes hair loss, and biochemical and biophysical properties of this drug are available [11]. This drug binds to plasma proteins in the blood, and only free drug concentration is available for uptake in the tissues. Free DOX concentration in the arterial blood is calculated as:

$$C_A = \frac{A_B}{V_B} \cdot (1 - F_B) \tag{4.1}$$

with V_B the volume of the blood compartment in [m^3], and F_B the fraction of DOX bound to plasma proteins, typically 0.7.

Doxorubicin is also able to bind to specific macromolecules in tissues (e.g. DNA), also showing Michaelis Menten Kinetics. To compensate for this, the venous return concentration is calculated as:

$$C_{V_i} = \frac{A_i}{V_i} - \frac{T_{\mathrm{DNA}} \cdot C_{V_i}}{K_{\mathrm{DNA}} + C_{V_i}}$$

in which T_{DNA} is the tissue–specific DNA binding capacity for DOX in [moles/m^3].

Temperature dependent blood flow obtained by the heat transfer model is used in the PBPK model as input parameter. The model then calculates the drug concentration in the hair follicle compartment. Finally, a statistical model is needed to be able to assess the amount of hair damage and to predict whether hair loss will occur.

5. Experiments on Hair Follicle Damage

In a study on Doxorubicin handling by kidney epithelial tissue, Decorti shows that Doxorubicin uptake is temperature dependent [13]. At 37°C, drug uptake in the kidney cells in one hour is 7 times higher than at 4°C. We would like to investigate these effects for drug uptake in the hair follicle using temperatures that are relevant for scalp cooling. But not only drug uptake, also hair follicle damage should be analyzed.

To gain more insight into the importance of both reduced drug supply and reduced drug actions, *in vitro* experiments will be conducted on the influence of both temperature and drug concentration on drug uptake and hair follicle damage. In this study, hair follicle damage is defined as the amount of anti–tumor protein p53 produced in the hair follicle. This protein is produced by hair follicles when damaged by cytotoxic drugs and is always present in chemotherapy-induced hair loss [12].

A preliminary protocol defines 4 different regimes to be studied, making combinations of either high (32–34°C) or low temperature (20–22°C) and low or high drug concentration. These low and high drug concentrations will be determined by the PBPK model with or without cooling, respectively. In addition, 2 control groups will be studied where drug concentration is zero. With these experiments, we hope to determine the relative importance of the two mechanisms to which the prevention of hair loss are attributed.

6. Results and Outlook

The aim of this study is to develop a biological and physiological model of scalp cooling, in order to identify the important aspects in scalp cooling. For this, numerical models for heat transfer, medicine transport and cell damage are being developed. Important aspect in this study is the mutual relationship between temperature and perfusion, since it is needed for the heat transfer model and to simulate medicine transport in the human body.

In a preliminary experiment, we investigated this relationship. The results show a negative threshold for relative perfusion (3.5°C), and subsequent the fitted Q_{10} value ($Q_{10} = 3.75$) is greater than any value cited in literature ($2 < Q_{10} < 3$). However, neglecting the threshold behavior and using Eq. (2.1), the perfusion reduction corresponds to a Q_{10} value of 2.65. This shows that further experiments are needed to investigate this threshold behavior and to establish the relation for the temperature dependence of perfusion.

Our heat transfer model shows that important parameters are the thermal resistances of both the fat and hair layer [9]. During cooling, the base model shows a skin temperature of 18°C and a factor 5 decrease in perfusion. Changing the thickness of the hair layer yields skin temperatures ranging from 22°C to 10°C, and perfusion may be reduced by a factor 3 to 15 from normal. Changes in the fat layer thickness, and changes in thermal conductivity of both fat and hair layer show similar results. This large variation in perfusion reduction shows that temperature should be as low as possible, yet still comfortable for the patients, to ensure that the amount of drugs delivered to the hair follicles is as low as possible.

The heat transfer model provides the necessary perfusion data for a Physiological Based Pharmacokinetic (PBPK) model. Using relative perfusion and temperatures of the scalp skin, the total amount of drugs that are delivered to the hair follicles can be calculated. A statistical model is needed to determine the resulting damage inflicted to the hair follicle. For this, experiments are to be conducted.

The fact that DOX uptake in kidney cells decreases with lower temperatures [13], independent of perfusion, poses an interesting starting point for further examination. In the near future, hair follicle experiments are to be conducted, to investigate the influence of drug uptake and hair follicle damage at relevant temperatures. Also, the influence of extracellular concentrations will be studied.

After experimental establishment of some of the primitive relations that are part of the chain of events preventing hair loss, the combination of sub–models will result in a complete model that can help in optimizing scalp cooling for hair loss prevention.

Acknowledgement

The authors would like to acknowledge the work and support of Dr. W.P.M. Breed. This research was sponsored by SOBU, an administrative cooperation between Tilburg University and the Eindhoven University of Technology.

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