Mathematical Modelling of Thermal and Circulatory Effects during Hemodialysis

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Intradialytic hypotension (IDH) is one of the most common complications of hemodialysis (HD) treatment. The initiating factor of IDH is a decrease in blood volume which is related to an imbalance between ultrafiltration (UF) and refilling rate. Impaired reactivity of resistance and capacitance vessels in reaction to hypovolemia plays possibly a major role in the occurrence of IDH. These vessels also fulfill an important function in body temperature regulation. UF induced cutaneous vasoconstriction would result in a reduced surface heat loss and an increase in core temperature. To release body heat, skin blood flow (SBF) is increased at a later stage of the HD treatment, whereby possibly IDH can occur. A mathematical procedure has been developed by coupling a thermo-physiological (TP) model with a cardiovascular (CV) model to study regulation mechanisms in the human body during HD+UF. Model simulations for isothermal vs. thermoneutral HD+UF were compared to measurement data of patients on chronic intermittent HD (n=13). Core temperature during simulated HD+UF sessions increased within the range of measurement data (0.23ºC vs. 0.32±0.41ºC). The model showed a decline in mean arterial pressure (MAP) of -7% for thermoneutral HD+UF versus -4% for isothermal HD+UF after 200 minutes during which relative blood volume (RBV) changed by -13%. In conclusion, simulation results of the combined model show possibilities for predicting circulatory and thermal responses during HD+UF.

Key words: Cardiovascular modelling, Hemodialysis, Hypotension, Thermoregulation

Introduction

Hemodialysis (HD) is the most common method used to treat kidney failure. Severe loss of kidney function is a threat to life and requires removal of toxic waste products and restoration of body fluid towards desired levels. This can be accomplished by dialysis with an artificial kidney. Excess body water, accumulated during the interdialytic period is removed by blood ultrafiltration (UF). Plasma water depletion induces a decline in relative blood volume (RBV) up to 20% in a 3-4 hour period, thereby disturbing the cardiovascular system. Autonomic compensatory responses to hypovolemia involve a decrease in venous vessel capacity to maintain cardiac filling, an increase in vascular resistance to ensure perfusion of critical organs and an increase in cardiac contractility and rate to optimize heart activity (3). Hypovolemia has been suggested to be the main initiating factor behind intradialytic hypotension (IDH). IDH remains a significant cause of morbidity and patient discomfort in the HD population since underlying mechanisms are not yet fully understood (1). Several theories have been introduced to explain IDH (7). These include: acute alterations in the autonomic nervous system activity, a decrease in plasma osmolality related to dialysate sodium concentration, a marked fall in cardiac output, impaired venous compliance and an impaired reactivity of capacitance and resistance vessels. The exact role of the capacitance and resistance vessels in the blood pressure response to HD remains uncertain. In general, an important function of these vessels is related to body temperature regulation. Heat loss across the skin surface is regulated by controlling blood flow in cutaneous blood vessels. In a warm environment the vessel’s diameter is widened. This provides an increase in blood flow to the periphery. As a result, skin temperature rises which leads to an increase in heat transfer to the environment. The opposite mechanism, occurring in a cold ambient, is called vasoconstriction and is defined as narrowing of the core to peripheral blood vessels by contraction of the vessel’s muscular wall. Gotch et al. (9) introduced the hypothesis that during HD, when resistance vessels are constricted due to loss in circulatory blood volume, the regular heat balance is interrupted by means of reduced heat dissipation from the skin, while at the same time the metabolic heat production remains the same. As a consequence heat is accumulated and core temperature would increase during the dialysis treatment. At a certain threshold skin vessels would open in order to remove excess heat from the body core. This mechanism counteracts the physiological response to hypovolemia, thereby possibly causing sudden hypotensive episodes during the HD session. Van der Sande et al. (2009) showed that the internal heat accumulation might very well be responsible for the impaired vascular response during HD and found that patient stability increases by cooling of the extracorporeal blood flow (27). These observations have led to growing
interest in thermal and circulatory effects during hemodialysis in the last few years since underlying mechanisms for an increase in core temperature, effect of dialysate temperature and IDH are not yet fully understood. The hypothesis by Gotch et al. has not yet been verified; in consequence we developed a mathematical model which accounts for thermal and hypervolemic effects on the cardiovascular system during HD+UF. Fundamentally, the procedure is based on a coupled thermo-cardiovascular model. This approach enables to examine the role of cutaneous vasomotion in the occurrence of IDH. Mathematical models with respect to arterial pressure response to blood volume withdrawal have been proposed by Cavalcanti et al. (3) and Ursino et al. (23) but to our knowledge no models exist where in addition also thermal effects were taken into account.

Physiological Models
To characterize physiological behavior of the human body related to thermal and cardiovascular response during HD, two models are considered: a thermo-physiological (TP) model and a cardiovascular (CV) model. Both models interact as illustrated in figure 1. Changes in heart rate (HR) and blood volume (BV) are used as model inputs. A reduction in HR leads to a decrease in cardiac output (CO). Plasma water removal reduces circulatory blood volume, after which right atrial pressure ($p_{ra}$) tends to decline. Low right atrial pressure decreases stroke volume and therefore CO (Frank Starling effect); as a consequence arterial pressure ($p_{a}$) drops. To compensate for low blood pressure, baroreceptors generate impulses to increase total peripheral resistance (TPR) by vasoconstriction and to decrease unstressed venous volume ($V_{un}$). These baroreceptor pathways are indicated by dotted lines in the scheme. Hypothalamus temperature ($T_{by}$) is considered as core temperature, which will decrease if TPR declines and vice versa.

The thermo-physiological (TP) model
During current research ThermoSEM (22) is used to simulate thermoregulation in human body. The model’s fundamentals are based on the Fiala model (6). From the mathematical point of view the human thermoregulation model can be separated into a passive system and a controlling active system.

Passive System
The passive system accounts for environmental heat exchange and the conduction within the body elements. A characteristic geometry of the humanoid was achieved by lumping the body into 19 segments: a sphere for the head and 18 cylinders symbolizing the trunk and limbs (figure 2). All segments consist of multiple concentric layers, representing different tissue types, from the inside out: bone, muscle, fat, inner skin and outer skin. The segments are divided into three sectors whereupon asymmetric boundary conditions can be applied.

Pennes (1948) (18) introduced a modification to the heat equation that accounts for metabolic heat generation and the exchange of thermal heat between flowing blood and surrounding tissue:

$$\rho c \frac{\partial T}{\partial t} = k \nabla^2 T + \rho_b c_b w_b \left( T_a - T \right) + q$$

(1)

where $\rho$, $c$ and $k$ are density, specific heat and thermal conductivity respectively. $T$ is the local tissue temperature and $T_a$ the temperature of the perfusing blood. $w$ is the volumetric perfusion rate, $q$ the metabolic heat production and subscript ‘b’ describes a blood property. Solving Pennes’ heat equation for the body elements requires information of thermal energy transfer between skin surface and environment by convection, radiation and evaporation. The model also includes convective heat transfer by the blood in the capillary beds (22). Systemic blood circulation has a tremendous influence on heat dissipation within the body. It prevents organs with high metabolic rates such as the brain to overheat. In the present model blood flow was modeled by a central blood pool from which the body elements receive warm blood whereafter blood exchanges heat with the cutaneous tissue before is flows back to the central blood pool (figure 2).

Active System
The human body is capable of keeping core temperature within close limits (36.8±0.6°C) (16). Body temperature is
regulated by nervous feedback systems, and operates through
temperature regulation centers located in the hypothalamus.
Output signals are used to balance heat production against heat
loss. Heat production is in principle a by-product of
metabolism. Temperature and heat production due to cell
metabolism are coupled with the van ’t Hoff \( Q_{10} \) relation,
which states that for every 10ºC decrease in tissue temperature
metabolism is reduced by a factor \( Q_{10} \). When the rate of
heat production in the body is higher than the rate at heat is
being lost, heat builds up in the body and as a consequence
core temperature rises. Conversely, when heat loss is higher,
body temperature decreases. In cold conditions the human
body reacts by means of shivering and vasocostriction. In a
warm environment the temperature control system uses
vasodilatation of skin blood vessels and sweating to release
body heat when body temperature becomes too high. All these
mechanisms are incorporated in the active system of the TP
model. The present active model operates with so called error
signals introduced by Stolwijk (24). An error signal equals the
difference between the actual state of a variable \( x \) and its
setpoint \( x_o \) where the model tries to minimize the error
functions.

**Perfusion**

In the bioheat equation (equation 1) \( w_b \) appears as the blood
perfusion rate. During thermoneutral conditions tissues are
supplied at a perfusion rate \( w_{b,0} \), in case of non-thermoneutral
conditions the flow \( w_b \) vary with changes in local metabolic
rates. Experiments from Rowell et al. (19) showed that
perfusion is linearly related to metabolism, therefore the
current model directly considers the energy equivalent
change in the factor \( \Delta \beta_i = \rho_b c_b \Delta w_{b,i} \) as a function of the change in
metabolism \( \Delta q_i \):

\[
\Delta \beta_i = \mu_b \Delta q_i \quad (2)
\]

Factor \( \mu_b \) was obtained from Stolwijk (24).

**Vasomotion**

The rate of blood flow into the skin venous plexus can vary
remarkably from barely zero to as great as 30% of the cardiac
output (11). By expressing the local skin blood flow \( (SBF_i) \) in
terms of the energy-equivalent \( \beta_i \) one obtains (7):

\[
\beta_i = \rho_b c_b SBF_i = \frac{\beta_i,0 + a_{di,j} DI}{1 + a_{ci},Cs \exp(-\eta DI)} Q_{10} \quad (3)
\]

Where \( \beta_i,0 \) arises from the basal skin blood flow; \( a_{ci} \) and \( a_{di} \)
distribution coefficients; \( T_{sk,i} \) and \( T_{sk,i,0} \) are the actual and
the reference skin temperature of the \( i \)-th skin sector and \( DI \)
and \( Cs \) represent the overall responses of peripheral
vasodilatation and vasocostriction respectively.
Vasoconstriction increases cutaneous resistance and therefore
reduces SBF. As a consequence heat is retained in the body
core. The expression for \( Cs \) was taken from Fiala (7).

\[
CS = 35 \left[ \tan \left( 0.34 \Delta T_{sk,m} + 1.07 \right) - 1 \right] \Delta T_{sk,m} + 3.9 \Delta T_{sk,m} \quad (4)
\]

In medium hot environments dilatation leads to an increase in
SBF which causes heat to be transferred from the core to the
skin, again also the expression for \( DI \) was taken from Fiala (7):

\[
DI = 21 \left[ \tanh \left( 0.79 \Delta T_{sk,m} - 0.70 \right) + 1 \right] \Delta T_{sk,m} + 32 \left[ \tanh \left( 3.29 \Delta T_{hy} - 1.46 \right) + 1 \right] \Delta T_{hy} \quad (5)
\]

**HD equipment heat exchange**

An extension of the TP model has been made for the
incorporation of HD equipment. Current research is focused
on thermal and cardiovascular response during HD treatment,
therefore only blood volume reduction by way of UF and
thermal effects of the HD equipment are modeled. In clinical
practice a blood temperature monitor controls the temperature
of the patient by adjusting the dialysate temperature. Several
methods have been introduced to control patient core
temperature, these include: thermoneutral (no energy transfer
from patient to extracorporeal circuit), constant core
temperature and constant dialysate temperature (26). The HD
heat exchange model controls the body’s core temperature by
controlling the blood temperature in the venous line. Energy
transfer \( ET \) can be calculated by use of equation 6 (25):

\[
ET = \rho_b c_b Q_{dia,b} \left( T_{dia,b,\text{out}} - T_{dia,b,\text{in}} \right) \quad (6)
\]

Where \( Q_{dia,b} \) the blood flow through the dialysis machine,
\( T_{dia,b,\text{in}} \) the ingoing blood temperature in the arterial line and
\( T_{dia,b,\text{out}} \) the outgoing temperature of the blood in the venous
line. In the original model, arterial blood exchanges heat by
convection in the capillary beds only. The venous blood
collects in the major veins and is re-warmed by heat from the
adjacent arteries as it flows back to the central blood pool. It
mixes with blood from other elements to produce the new central
blood pool temperature. In the modified TP model with HD
heat exchange, a part of the cardiac output equal to \( Q_{dia,b} \) with
temperature \( T_{dia,b,\text{out}} \) assumed to mix with blood coming
from all other body parts before it flows back to the central
blood pool (figure 4). \( T_{dia,b,\text{out}} \) is lowered by the control model
when \( T_{hy} \) exceeds its baseline value. This concept allows the
incorporation of the heat exchange by the HD equipment.

**Cardiovascular (CV) Model**

In order to analyze the cardiovascular response to
hypovolemia, Cavalcanti et al. (2) developed a mathematical
model to simulate arterial blood pressure changes induced by
HD+UF. Changes in HR and blood volume reduction obtained
by measurements were used as model inputs. They proposed a
physiological based procedure able to reproduce patient
specific measurement data during HD sessions (CO, TPR and
change in unstressed venous volume) by fitting three patient
dependent sensitivity variables \( (K_{aff}, K_i, K_v) \) with an iteration
algorithm. In this model the cardiovascular system is
described by Guyton’s classical models (10) based on the
Windkessel theory by Otto Frank (8). The systemic circulation
is lumped in a few compartments to itemize only the most
relevant circulatory districts. Current CV model is based on

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this model proposed by Cavalcanti et al. (2) where it has been extended with additional temperature dependent resistances for the cutaneous and arteriole circulation. By means of this concept thermal effects on the cardiovascular system are incorporated. A patient specific compartment has been added for the arteriovenous fistula (Figure 3). The original iterative character is adapted by assuming the three patient dependent variables in advance to achieve a predictive model behavior. To mimic the main short time pressure regulatory mechanisms, the model includes Starling’s law, inotropic heart regulation and baroreflex control of resistance and capacitance vessels. When the cardiovascular system is stressed by the loss of circulatory blood volume, as occurring during HD+UF, venous capacity can actively be constricted. This mechanism compensates for changes in circulatory blood volume due to an increase in vasomotor tone (4). In particular, splanchnic and cutaneous vessels have a variable blood storage function. Increased TPR during hypovolemia raises pressure in the arterial circulation. When blood volume declines, a rise in HR can also compensate for a drop in arterial pressure.

**Cardiac pump**

Because the hemodynamic response under study involves much slower dynamics than the HR period, the heart is modeled as a continuous pump, hence neglecting the pulsating nature of the cardiac pump. The CV model’s cardiac output $Q_{co,cv}$ is expressed by relationship (4):

$$Q_{co,cv} = Q_{sat} \left[1 - \exp \left(-\frac{p_{ran} - p_{ran}}{p_{ran}}\right)\right]$$

in which, $Q_{sat}$ the saturation level, $p_{ran}$ the right atrial pressure, $p_{ran}$ the pressure for null CO and $p_{ran}$ a sensitivity parameter that determines the sensitivity of CO to right atrial pressure (4). The inotropic effect of the heart is taken into account by a sigmoid function of the HR, which modulates the saturation level ($Q_{sat}$) of the cardiac curve (4):

$$Q_{sat} = Q_m \left[1 + 3 \cdot K_{co} \cdot \tanh \left(2 \cdot \frac{f - f_e}{f_e}\right)\right]$$

With $Q_m$ the maximum cardiac output at the beginning of the simulation, $f$ the current HR and $f_e$ the HR at the beginning of the dialysis. $K_{co}$ represent the sensitivity parameter of HR to $Q_{sat}$. By way of using these two expressions a proper fit on dynamic physiological heart curve data is accomplished.

**Systemic circulation**

The model as shown in Figure 3 shows in an anatomical sense the blood flow from the heart to the aorta which branches in several medium sized arteries and in the thermo-sensitive arterioles with variable resistance $R_a$. Compartments in parallel arrangement represent the resistance vessels. They account for the systemic capillaries in the cutaneous and splanchnic region whereas the fistula can be considered as a bypass of the latter. Venous circulation starts with the venules and medium sized veins from where the blood ultimately discharges into the inferior vena cava.

The mathematical circulatory system model consists of six compartments, respectively: right atrium (ra), arterial (a), microcirculatory (m), skin (sk), fistula (f) and venous (v). Each compartment is modeled as an elastic chamber with a specific volume and compliance $C_i$ to account for the capacitive properties of the circulation. Blood can flow in or out these compartments through hydraulic resistances. Shaded elements in the figure indicate time varying quantities under regulation. In general, each compartment of the cardiovascular system can be described by its resistance to flow $R_i$ defined by the relation:

$$Q_i = \frac{\Delta p_i}{R_i}$$

where $\Delta p_i$ is the pressure drop between the two compartments and $Q_i$ the flow through the resistance $R_i$ which links them. The system of ordinary differential equations describing the CV model dynamics is obtained by applying the law of mass conservation:

$$\frac{dV_i}{dt} = Q_{co,cv} - \frac{P_a - P_m}{R_{eq}}$$

As the heart fills with less blood than usual, the force of cardiac muscular contractions decreases. This is a result of a decrease in the load experienced by the heart muscle fibre due to the lower amount of blood entering the heart. Changes in inotropic heart activity produce considerable changes in stroke volume which is known as the Frank Starling effect. This effect is predominantly responsible for the decrease in CO during HD+UF.

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**Figure 3: Hydraulic equivalent of the cardiovascular model.** The heart with heart rate (HR) is represented by a single compartment (right atrium) as a continuous pump. The compliances are depicted by $C_i$ (with $i$ = arterial (a), microcirculatory (m), skin (sk), fistula (f), venous (v), or right atrium (ra)), the resistances by $R_i$, and the pressures in each compartment by $p_i$. Only the shaded elements are affected by regulation mechanisms.
\[
\frac{d(V_i + V_{sk} + V_f)}{dt} = \frac{p_a - p_m}{R_e} - \frac{p_m - p_v}{R_v}
\] (11)

\[
\frac{dV_{ra}}{dt} = \frac{p_v - p_{ra}}{R_{ra}} - Q_{co, cv}
\] (12)

In this set of equations, \(Q_{co, cv}\) is the CV model’s cardiac output described by equation 7. \(V_i\) represents the compartment volume, \(R_e\) the resistance, and \(p_i\) the pressure. Due to the parallel arrangement of the microcirculatory, fistula and skin compartment, the pressures in there are equal. Before solving the system, \(R_{eq}\) is calculated as the equivalent resistance between the arterial and parallel chambers:

\[
R_{eq} = R_a + \left(\frac{1}{R_{ra}} + \frac{1}{R_{sk}} + \frac{1}{R_i}\right)^{-1}
\] (13)

Model equations were solved numerically using the one step Adams-Bashforth method with constant time step. For each compartment pressure is calculated by:

\[
p_i = \frac{V_i - V_{ia}}{C_i} \quad \text{with } i = a, eq, v, ra \text{ for } V_i \geq V_{ia}
\] (14)

In which \(V_{ia}\) the unstressed volume of compartment \(i\). Arterial pressure \(p_a\) was in accordance with the original model considered as mean arterial pressure (MAP).

**Baroreflex control**

The compensatory mechanisms are initiated by two types of receptors: one by cardiopulmonary baroreceptors located in the atria and the main pulmonary veins, the other by arterial baroreceptors located in the aortic arch and in carotid sinus. In case of low blood pressure the cardiopulmonary and arterial baroreceptors discharge leads to the generation of efferent signals, affecting the cardiovascular system parameters (i.e. HR and contractility, microcirculatory resistance \(R_m\), skin resistance \(R_{sk}\)) and unstressed venous volume \(V_{vu}\) (3). Variations of \(p_a\) and \(p_{ra}\) are compared with the values at the beginning of the treatment to actuate the static vasomotor tone \(\theta_s\), as shown in equation 15:

\[
\theta_s = (1 - K_{aff}) \frac{p_a - p_{ae}}{p_{ae}} + (1 + K_{aff}) \frac{p_{ra} - p_{rae}}{p_{rae}}
\] (15)

Where \(p_{ae}\) and \(p_{rae}\) indicate arterial and atrial pressure at the beginning of the dialysis, when the cardiovascular system is in equilibrium. By changing the model parameter \(K_{aff}\) from -1 to 1, a different relative weight can be assigned to the afferents. When \(K_{aff}\) is equal to -1 the cardiopulmonary afferent is completely inhibited and the control is executed by the arterial side only. When \(K_{aff}\) is equal to 0 the afferents are exactly balanced. The typical baroreflex control dynamics are modeled with a first order filter (equation 16) where \(r\) is a time constant.

\[
\frac{d\theta_d}{dt} = \frac{1}{\tau} (\theta_s - \theta_d)
\] (16)

Efferent regulations were modeled by sigmoid functions suitable for obtaining linear behavior for small pressure perturbations and the typical saturation effects for large perturbations (4):

\[
R_m = R_{me}[1 - K_r \tan(2\theta_d)]
\] (17)

\[
V_{vu} = V_{vuc}[1 + K_v \tan(2\theta_d)]
\] (18)

With \(V_{vuc}\) and \(R_{me}\) the unstressed venous volume and the microcirculatory resistance at the beginning of the dialysis when \(\theta_d\) equals 0. The balance parameter \(K_{aff}\) of the afferent pathways and the gains \(K_r\) and \(K_v\) express the efficiency in the overall regulation of vasoconstriction. The values of \(K_{aff}\), \(K_r\) and \(K_v\) were assumed a priori. By doing this, patient dependent properties can be incorporated. At last new values for \(V_{vu}\) and \(R_m\) for the next time step are obtained.

**Coupling of Cardiovascular and Thermo-Physiological model**

Cardiovascular reactivity closely depends on changes in thermal state of the body and vice versa. Hypovolemic induced cutaneous vasoconstriction in the TP model is achieved by incorporation of baroreceptor signals from the atrial and arterial compartment (figure 4). These signals are translated to dynamic vasomotor tone \(\theta_d\). In the CV model thermo sensitive resistances have been added. Cutaneous resistance \(R_{sk}\) and arteriole resistance \(R_a\) are forced to vary with total SBF predicted by the TP model. Hence, blood pressure changes can be predicted as a consequence of alterations in hypothalamus temperature \(T_{hy}\). Heat withdrawal and blood flow through the dialysis machine is visualized by the zigzag line (figure 4).

Figure 4: Schematic interaction between both models. Baroreceptor pressure signals as a function of right atrial pressure \(p_{a_d}\) and arterial pressure \(p_a\) are transferred by \(\theta_d\) to the TP model where they alter the vasoconstriction \((Cs)\) function. Body temperature dependent SBF predicted by the TP model is used to adjust skin resistance \(R_{sk}\) and arteriole resistance \(R_a\). Heat withdrawal and blood flow through the HD machine is indicated by the zigzag line.

**Thermal to Cardiovascular**

Heat transfer to the skin by the blood is controlled by the degree of vasoconstriction of the arterioles and the arteriovenous anastomoses that supply blood to the venous plexus of the skin. Constriction of these vessels affects total peripheral resistance and thereby MAP. Modelling this...
mechanism is achieved by adding two additional body temperature dependent resistances \( R_{sk}(\Delta T_{sk}, \Delta T_{sk}) \) and \( R_{ac}(\Delta T_{ac}, \Delta T_{ac}) \) to the original Cavalcanti model (3) (figure 3). \( R_{sk} \) represents resistance to flow through the systemic cutaneous circulation and \( R_{ac} \) the arteriole resistance at the end of the aorta. Since they are closely related in cutaneous blood flow regulation, \( R_{sk} \) is assumed to vary linear proportional with \( R_{ac} \) as a first assumption: \( R_{sk} = \varphi R_{ac} \) where \( \varphi \) is introduced as proportionality factor. During HD+UF, CO can decrease up to 40% (27). This phenomenon is incorporated in the cardiac curve of the CV model, in contrast to the TP model where constant CO is assumed. For this reason skin blood flow from the TP model is scaled to the CO predicted by the CV model on each timestep. Hence, an underlying assumption in here is that SBF redistribution is linear proportional with the decrease in CO in the course of the HD procedure. This approach enables to translate changes in SBF in the TP model to the CV model where the corresponding resistance is calculated to fit the scaled SBF for each time step:

\[
R_{sk} = \frac{R_{ac} R_{m} (Q_{co,cv} - Q_{sk,cv})}{Q_{sk,cv} (R_{ac} + R_{m})}
\] (19)

In which the scaled skin blood flow is:

\[
Q_{sk,cv} = \frac{Q_{sk,ip} Q_{co,cv}}{Q_{co,cv,0}}
\] (20)

In this equation \( Q_{co,cv} \) is the current CO on timestep \( t \) and \( Q_{co,cv,0} \) the CO at the beginning of the dialysis when the CV system is in stationary state, the ratio between them can be considered as a scale factor. \( Q_{sk,ip} \) is the SBF simulated by the TP model for a certain thermal state of the body.

Cardiovascular to Thermal

In hypovolemic state, reflexes from baroreceptors stimulate the vasoconstrictor system throughout the body including blood vessels in the cutaneous circulation (12). Figure 5 shows how static vasomotor tone \( \theta_i \) is transformed to typical dynamic vasomotor tone \( \theta_d \) by a low pass filter. Sigmoid functions account for change in unstressed venous volume, microcirculatory resistance and the vasoconstriction equation \( (Cs) \) as a function of \( \theta_d \). To incorporate hypovolemic induced cutaneous vasoconstriction, an adaption has been made on the \( Cs \) function in the TP model:

\[
Cs = 35 \left[ \tanh \left( 0.34 \Delta T_{sk,m} + 1.07 \right) - 1 \right] \Delta T_{sk,m} + 3.9 \Delta T_{sk,m} \frac{d\theta_{k,m}}{dt} + K_{cs} \tanh \left( \alpha_{cs} \theta_d \right)
\] (21)

The sigmoid function on the right hand side of equation 21 has been added to equation 4. This concept allows forcing the SBF to change in accordance with experimental data (26) during thermonuclear HD+UF, where the factor \( K_{cs} \) determines the saturation level and \( \alpha_{cs} \) the gradient of the curve. Hence these coefficients determine indirectly the amount of hypovolemic induced SBF reduction during treatment.

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**Figure 5:** Static vasomotor tone signal \( \theta_i \) is translated via a low pass filter into dynamic vasomotor tone \( \theta_d \) which incorporates the typical dynamics of vasomotor regulation. Thereafter unstressed volume, microcirculatory resistance and the vasoconstriction function \( (Cs) \) are adapted. Dark grey frame: CV model, grey frame: TP model.

**Initial and parameter value assignment**

To accomplish a physiological realistic numerical simulation, a strategy for assigning values to model parameters was established. All parameter values were verified to correspond with physiological data. For the CV model constants are based on Cavani 2001 (4), for data values regarding the TP model a reference is made to Severens 2008 (22). Heart curve, initial mean arterial pressure \( (MAP_0) \) and baroreflex control parameters were assigned \emph{a priori}. HR data and the decline in blood volume during treatment were used as model inputs. Decay in total blood volume was prescribed linearly which, according to experimental evidence turns out to be a reasonable assumption (14). HR was assumed constant in time since mean experimental data shows a comparable trend (26).

As a starting point heart curve parameters in equation 7 were identified to obtain the best fit on cardiac curves from physiological data. Furthermore, the percentage of distribution between the six compartments as well as compliance values \( C_i \) were determined in accordance with human physiological data similar to those used in previous studies (2) (table 1). Total circulatory blood volume was estimated with respect to patient body weight \( (52 \text{ ml/kg}) \) (2).

**Table 1:** Initial blood volume \( (V_i) \) percentage distribution, resistance values \( (R_i) \) and compliance values \( (C_i) \).

<table>
<thead>
<tr>
<th>Compartment</th>
<th>( V_i ) [%]</th>
<th>( R_i ) [mmHg·s·ml(^{-1})]</th>
<th>( C_i ) [ml·mmHg(^{-1})]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial</td>
<td>18</td>
<td>0.16</td>
<td>1.0</td>
</tr>
<tr>
<td>Microcirculatory</td>
<td>4</td>
<td>0.6</td>
<td>9.2</td>
</tr>
<tr>
<td>Venous</td>
<td>59</td>
<td>0.22</td>
<td>20.6</td>
</tr>
<tr>
<td>Atrial</td>
<td>13</td>
<td>0.09</td>
<td>33.1</td>
</tr>
<tr>
<td>Skin</td>
<td>6</td>
<td>9.0</td>
<td>9.2</td>
</tr>
<tr>
<td>Fistula</td>
<td>0</td>
<td>3.6</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Unstressed volume of the arterial compartment \( V_{au} \) originates from the initial arterial pressure \( p_{ae} \) and equation 14. Unstressed volume in the microcirculatory compartment \( V_{mu} \) was 4.5 ml/kg body weight (2). The unstressed volume of the right atrium \( V_{rau} \) was calculated with use of equation 14 by substituting the right atrial pressure when the cardiovascular
system is in equilibrium at the beginning of the dialysis when venous return equals CO. Volume of the fistula $V_f$ was assumed to be very small compared to the total blood volume ($V_{tot}$) and was therefore neglected. Compliance of the fistula $C_f$ was assumed to be close to zero because the vessel's wall becomes very stiff as the fistula matures. To estimate cutaneous compliance the same value was taken as for the microcirculation. Finally, values for resistances $R_i$ with $i=eq$, $v$, $ra$ were obtained by imposing the equilibrium condition of the model at the beginning of the dialysis. $R_f$ was chosen to fit a typical fistula flow (1.0 l/min). The initial value for cutaneous resistance $R_{skc}$ is calculated to fit basal SBF predicted by the TP model for a person in thermal neutral condition when the cardiovascular system is in stationary state. Experimental data (13) of thermal induced blood pressure changes was used to determine proportionality factor $\phi$ by fitting this coefficient on the amplitude of MAP. The three baroreflex control parameters were selected to best fit the mean dialysis data for stable subjects obtained from Van der Sande et al. (26). Distribution coefficients $a_v$ and $a_d$ of all body parts were assumed to be the same as in Fiala 2001 (7), implying that hypovolemic cutaneous vasoconstriction over all body parts is assumed to react the same as in case of thermal induced vasoconstriction.

Thermal induced blood pressure changes (validation 1)

To validate the CV model with thermal effects, experimental data obtained in a climate tent setup (13) is compared to simulated blood pressure in response to heating and cooling. The subgroup of elderly was chosen because they best reflect the HD population group. Main objective is validating the CV model towards predicting blood pressure changes caused by heating and cooling. The fistula is omitted in the simulations since experimental data is obtained from healthy subjects, hence $R_f \rightarrow \infty$.

Materials and methods

Twelve healthy elderly men volunteers participated in the study. Two were rejected because an incomplete dataset was obtained. Ultimately, ten subjects (age=70.9±4.2 yr) were included. They stayed in a climate tent (CAT-430 Colorado Altitude Training, USA) for 3.5 hours in supine position. Air temperature was controlled by means of two air heaters and one air conditioner unit. Blood pressure was measured every 10 minutes with a digital sphygmomanometer with automatic inflation (Cresta Taiwan). Subjects were exposed to temperature protocols P1 and P2 (figure 6). The study protocol was approved by Maastricht University Medical Ethical Committee. For a more detailed description of these experiments a reference is made to (13).

Results

Protocols P1 & P2 were simulated by the combined TP-CV model. Since the mean arterial pressure at the beginning of the measurements (MAP$_0$) was different for each subject, MAP was normalized for this initial value. Results for simulated MAP are presented in figure 6. Measurement data points (±SD) are plotted in the same graph as well.

![Figure 6: Validation study. Normalized MAP: simulation vs. experiment, elderly subjects (n=10), protocol for ambient air temperature P1 (top) & P2 (bottom).](image)

In protocol P1, MAP remains constant in the first 30 minutes since the subject is in thermal neutral state. Ambient air temperature decreases to 20ºC over a 15 minute period after which blood pressure rises as a consequence of vasoconstriction. Gradient of MAP is highly dependent on arterial compliance where a low compliance is characteristic for a steep gradient. MAP keeps on rising for the next 60 minutes with a lower gradient because skin blood flow approaches its minimal value. When ambient air temperature is changing to 35ºC less vasoconstriction is observed, resulting in a decreased MAP. On moment $t=150$ min. ambient air temperature is just declining to 30ºC where vasoconstriction causes the blood pressure to increase.

The second protocol (P2) is equal to P1 in the first 30 minutes. In the next stage of the experiment air temperature is set to 35ºC. In this period sweating is observed whereby skin temperature is restrained to rise excessively, this explains the minor change in MAP over this period. Blood pressure increases again due to vasoconstriction when ambient air temperature approaches 20ºC and declines again in the 30ºC phase to a value above baseline.

Hemodialysis combined with Ultrafiltration (validation 2)

The TP-CV model can ultimately be applied to HD+UF while accounting for thermal and hypovolemic effects on the cardiovascular system. Simulations and measurements were done for thermoneutral dialysis where no energy is transferred from patient to extracorporeal circuit (ET=0) as well as for
isothermal dialysis in which core temperature is kept constant ($\Delta T_{hy}=0$) by adjusting the blood temperature in the venous line.

**Materials and Methods**

Thirteen stable patients (age 55.23±13.5 yr) on chronic intermittent HD were studied (26). High-efficiency HD was delivered by volumetric machines (A2008H; Fresenius Medical Care, Walnut Creek, CA) and polysulfone dialyzers (F8 and F80; Fresenius Medical Care) using ultrapure bicarbonate dialysate (Diasafe; Fresenius Medical Care). Blood flow was 400 ml-min$^{-1}$, and dialysate flow was 800 ml-min$^{-1}$. Arterial and venous blood line temperatures, core temperature and energy transfer between the extracorporeal circuit and the patient were monitored noninvasively by a blood temperature monitor (Fresenius Medical Care, Bad Homburg, Germany). Changes in blood volume were monitored continuously and noninvasively with the Fresenius blood volume monitor (Fresenius Medical Care). The ambient air temperature was 23°C and relative humidity 40% for the mathematical model. Assumptions have been made on input values for wall temperature ($23^\circ$C), airspeed (0.05 m/s) and initial shunt flow (1.0 l/min) since measurement data was lacking.

**Results**

In figure 7 a-h final results for circulatory and thermal response of isothermal vs. thermoneutral HD+UF are presented. Dark grey lines indicate thermoneutral dialysis where no energy transfer between patient and extracorporeal circuit takes place (ET=0). Grey lines represent isothermal dialysis $\Delta T_{hy}=0$. Experimental dataplots (mean ±SD) obtained from Van der Sande et al. (26) are plotted in the corresponding graph. For clarity only one side of the error bar is visualized. Measurements were performed at the beginning, halfway and at the end of the HD treatment. Horizontal error bars indicate the time variation between the measurement points.
Blood volume is used as model input. Based on experimental data (14) blood volume is set to decline by 20% in a 5 hour timeframe for both sessions (figure 7a). HR was assumed to be constant in time since the same trend in mean experimental data was observed (26) (figure 7b). During thermoneutral dialysis simulated core temperature difference was predicted to be 0.23°C vs. 0.32 ± 0.41°C by measurements (figure 7c). Simulated skin temperature (T_{sk}) of the anterior side of the forearm (figure 7d) shows a reduction in both sessions ($\Delta T_{sk} = -0.52°C$ for ET=0 and $\Delta T_{sk} = -1.84°C$ for $\Delta T_{hy}=0$). The slope discontinuity in skin temperature just after 100 minutes during the thermoneural session was caused by moderate sweating activated by the increase in core temperature. In case of isothermal HD+UF core temperature is kept constant by way of controlling the extracorporeal blood temperature. Model calculations showed that an average rate of -8.7 W was transferred to keep core temperature constant. In clinical practice mean ET rate was -18.8 ± 10.9 W. Energy transfer was set to be zero for thermoneutral dialysis in the model, despite the same setting in the clinical situation change in ET was -2.6 ± 7.6 W (figure 7e). Oscillations in the grey lines originate from the disalsate temperature control model. Blood cooling inhibits an increase in the $DL$ value totally. As a consequence TPR raises more in isothermal dialysis. Absolute values for TPR are in the same order as measured, as well as the rate of change. Although a clear difference in TPR end value is simulated between $\Delta T_{hy}=0$ and ET=0 ($\Delta$TPR=0.23 mmHg·s·ml$^{-1}$), No significant difference can be found in the experimental data ($p=0.294$) (figure 7f). A rise in TPR lowers pressure in the right atrium and results in a decrease in CO in the course of the treatment. Prediction of CO in thermoneutral situation is close to mean experimental data values (figure 7g). Due to a higher TPR predicted by the model in isothermal case, CO is lower over the whole domain than measured in the isothermal case. Experimental data in the $\Delta T_{hy}=0$ procedure shows higher values for CO than the model simulations (6.27 ± 1.4 to 4.5 ± 1.1 l/min vs. 5.9 to 3.8 l/min after 200 minutes). Venous volume changed by -28% for simulation with constant core temperature compared to -29% without energy transfer. All former variables finally determining MAP for which a normalized plot is presented (figure 7h). While plasma water depletion occurs, overcompensation of regulation mechanisms causes blood pressure to rise in the first 50 minutes. Thereafter a progressive fall in blood pressure is predicted. Measurement data describes a large range of distribution for blood pressure response; mean average values show a higher blood pressure in case core temperature is kept constant, especially in the first 100 minutes. After 200 minutes MAP has changed by -8 ± 9%
during thermoneutral HD+UF where simulation predicts -7%. During isothermal treatment MAP changed by -10 ±12 % vs. -4% simulated after 200 minutes.

Discussion

The model predicted cardiac output (CO), total peripheral resistance (TPR) and mean arterial pressure (MAP) within the range of experimental data. Measured values for TPR presented showed no significant difference between isothermal (ΔTₚ=0) and thermoneutral (ET=0) dialysis sessions (p=0.294). CO measurements were higher in the isothermal case, indicating this was the main reason for a better preserved blood pressure. The model predicted clearly a higher TPR during isothermal dialysis and a lower CO. Selby et al. (21) compared the cardiovascular response for HD+UF with two different dialysate temperatures (37°C and 35°C). They came up with the same observed trend, suggesting an increase in TPR is indeed (also) responsible for a better preserved MAP during isothermal dialysis. HR was according to data obtained from Selby et al. lower for a dialysate temperature of 35°C. This observation can possibly explain why CO is predicted only slightly lower by the model compared to data from Selby et al.. However, simulation showed an almost negligible change in CO when HR was set to change linearly by +20 beats/min and -20 beats/min in 300 minutes with a decline in RBV of 20%. This observation is also in agreement with literature, where a decrease in CO during rest and hypovolemia is almost completely explained by a change in stroke volume (11).

Main challenge in modelling and validating thermal effects during hypovolemia is the combined effect of baroreceptors and thermoreceptors on (skin) blood flow regulation. Reduction in CO and an increase in TPR are responsible for alterations in SBF. The exact way of blood flow redistribution in these conditions remains uncertain. SBF is measured in clinical practice with Laser-Doppler devices. These measure relative changes in SBF locally, which makes verifying variations in total SBF during HD very hard to interpret. Moreover, useful measurement data in this field is still lacking. Simulation for the climate tent experiments showed that the model was able to predict blood pressure changes for the heating and cooling protocols in the range of measurement data. An important observation was the good agreement of the typical higher blood pressure end value compared to baseline.

Total difference in core temperature over the treatment period was lower predicted by the model, suggesting that also other factors play a role with respect to core temperature increase during HD+UF. Note that only thermal and cardiovascular effects caused by UF have been modelled, hence no effects by the HD treatment itself. Observations in clinical studies showed also an increase in core temperature during isovolemic HD (26). Furthermore, decrease in core temperature was more distinct during isolated UF compared to HD+UF for the same removed energy (25). Less energy had to be removed compared to experimental data to keep core temperature on baseline level. From this point of view it seems that hypovolemic vasoconstriction itself, theoretically, can be responsible for a substantial rise in core temperature (figure 7c). It should be noted that hypovolemic induced cutaneous vasoconstriction is assumed to react equally on the same skin areas as thermal induced vasoconstriction would do, although the exact response on SBF alterations during hypovolemia is still under debate (15). Due to the exploratory character of this research patient dependent constants in the TP model were chosen for a standard person. In the CV model these constants were obtained to correlate with mean values of measurements while in clinical practice each patient reacts differently, which makes it difficult to observe patient specific thermal and cardiovascular trends in simulated results. Both models have extensively been validated separately (5,3). They have proven to correlate well with experimental data for a wide range of subjects. Since the model developed in this study showed good agreement with mean measurement data, future research should be focused on incorporation and validation of patient specific characteristics.

No indications of sudden vasodilatation were observed in the simulations executed. Since the exact interaction between baro- and thermoreceptors is not yet fully understood a simulation was done for the hypothetical scenario when a sudden increase in SBF would occur due to sudden vasodilatation. When total SBF was set to increase from 0.2 l/min to 1 l/min after 260 min. in 20 minute period, MAP decreased by an additional 15% (figure 8), which is comparable to values observed in clinical practice. If an increase in CO cannot compensate for the extra need for SBF dangerous hypotension can occur.

![Figure 8: Effect on MAP by an increase in SBF from 0.2 l/min to 1 l/min after 260 minutes due to sudden vasodilatation.](image)

Conclusions

In this study a mathematical model is developed to examine thermal and circulatory effects during HD+UF by coupling a thermo-physiological model with a simple model of the cardiovascular system. Simulation results of the combined model have shown possibilities for predicting circulatory and thermal response during HD+UF. On the long term this model can help in clinical practice to determine an ideal treatment protocol for each individual patient to minimize complications. In addition, the model can potentially be used for preventing IDH in the course of HD. Validation of the coupled model for blood pressure changes caused by variations in ambient temperature offered promising results.
Primary hypothesis of this study suggested that UF-induced vasoconstriction would result in a reduction of SBF, a decrease in surface heat loss, increase in core temperature, rise in cutaneous blood flow and finally IDH. Indeed, when cutaneous vasoconstriction was activated for a person with regular clothing in a 23°C room, the model showed an increase in core temperature of almost 0.3ºC within 300 minutes. This indicates that reduced heat loss from the skin due to vasoconstriction per se can be responsible for a rise in core temperature during HD in the same order as measurements show. Simulation results revealed that an increase in blood flow to the periphery lowers blood pressure substantially but indications for sudden onset of this increased blood flow were not observed. In conclusion, this exploratory study has led to a new simulation model for hypovolemic induced cardiovascular changes while accounting for thermal effects in the course of HD+UF.

### Acknowledgements

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### Conflict of interest

None declared.

### Appendix

#### Model constants

**TP model**

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N.B. additional TP-model parameter values are registered in Severens 2008 (22).

#### CV model

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### Bibliography


