A mathematical model of life-threatening hyperthermia during infancy

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JARDINE, DAVID S. *A mathematical model of life-threatening hyperthermia during infancy.* J. Appl. Physiol. 73(1): 329–339, 1992.—A mathematical model was created to test the hypothesis that a partially covered febrile infant may develop potentially lethal temperature elevation. Infants may be at special risk to develop hyperthermia because, unlike older children, infants may not be able to remove blankets in response to temperature elevation. The model compared heat production ($\dot{M}_{T_{sk}}$) with heat loss ($\dot{Q}_{tot}$). The difference between these terms is the excess energy ($\dot{E}$): $\dot{M}_{T_{sk}} - \dot{Q}_{tot} = \dot{E}$. In most situations the simulated infant transfers heat to the environment as rapidly as it is produced ($\dot{E} < 0$), so hyperthermia does not result. In some situations, heat production exceeds heat loss ($\dot{E} > 0$), causing progressive warming. The time was calculated for the simulated infant to progress from 41 to 43.4°C (defined as a lethal end point). In certain circumstances, this may occur in <90 min. An infant at high risk of hyperthermia may not appear to be covered by a conspicuous excess of insulation (≤3.5 cm may be sufficient). In many situations, heat loss is more closely determined by exposed body surface area than by blanket thickness. These findings have important implications for understanding the antecedents of hyperthermia in infants and may help in understanding the role of hyperthermia in certain pediatric illnesses.

hyperpyrexia; heatstroke; sudden infant death; hemorrhagic shock and encephalopathy; computer model

FEVER RARELY PRODUCES temperatures >41.1°C (13, 46). Hypothalamic and medullary thermoregulatory centers provide redundant control that prevents body temperature from exceeding this maximum (31), probably because thermal injury occurs above this temperature (22, 27, 53). These central mechanisms control body temperature by regulating heat transfer to the environment and, to a lesser extent, by limiting endogenous heat production. The mechanisms of heat transfer include evaporation (sweating), convection, conduction, and radiation. Normally, these mechanisms can transfer endogenous heat to the environment more rapidly than it is produced, ensuring that severe hyperthermia does not occur. However, if bedding and clothing hinder efficient transfer of endogenous heat to the environment, hyperthermia may result (20). This risk is especially high if the body temperature is already elevated when the bedding is applied (39).

Infants are unable to remove their blankets in response to overheating. Some sleeping infants may not even arouse in response to environmentally induced hyperthermia (40). A sleeping covered infant may be at risk of injury from hyperthermia, especially if he should develop a fever in response to an infection. A recent mathematical model of thermal balance suggested that hyperthermia could occur in a sleeping infant and may be related to sleeping position (36). This model did not define the time required to reach harmful temperatures.

To learn more about the risk of hyperthermia in a sleeping partially covered infant, a mathematical model of heat balance was designed.[1] The model quantifies metabolic heat production and heat loss from conduction, convection, radiation, and evaporation. When heat production exceeds heat loss, body temperature must rise (termed "thermal entrapment"). By use of the model, a variety of different environmental circumstances can be quickly evaluated for the risk of thermal entrapment and lethal hyperthermia.

This mathematical model was used to answer three questions: *1*) Is it possible for an infant to be thermally entrapped? *2*) If the infant is thermally entrapped, how long will it take to reach lethal hyperthermia [defined as 43.4°C (110°F)]? *3*) Would the environmental circumstances causing thermal entrapment be so unusual that they would be easily recognized?

METHODS

For simplicity, the total quantity of insulation overlying an infant (clothing and bedding) is referred to as "blankets."

Heat transfer to the environment occurs at the body surface. This model used 16 variables to explore the effect of various situations on heat transfer to the environment (Table 1). The effect of these variables is analyzed by comparing heat production with the sum of heat loss from radiation, convection, conduction, and evaporation. The difference between heat production and heat loss is defined as excess energy

$$\dot{M}_{T_{sk}} - \dot{Q}_{tot} = \dot{E} \qquad (1)$$

where $\dot{M}_{T_{sk}}$ is basal metabolic rate (BMR) at body temperature, T_{sk} (W); $\dot{Q}_{tot}$ is total heat loss, all routes (W); and $\dot{E}$ is excess energy (W).

If $\dot{E}$ is >0, the infant is unable to transfer heat to the

[1] The mathematical model is available from the author in the form of a spreadsheet for Microsoft Excel for Macintosh or IBM-compatible personal computers. Requests for a copy of the model should include a formatted 3.5-in. disk and a self-addressed stamped envelope.

TABLE 1. *Model variables that may be manipulated*

Variable	Symbol	Units	$\dot{Q}$	$\dot{M}$
Atmospheric temperature	T_a	°C	*	
Ambient vapor pressure	$P_{w,a}$	Torr	*	
Blanket thickness	b	m	*	
Blanket thermal conductivity constant	τ	$W \cdot m^{-1} \cdot °C^{-1}$	*	
Mattress thickness	b	m	*	
Mattress thermal conductivity constant	τ	$W \cdot m^{-1} \cdot °C^{-1}$	*	
%Body surface exposed to blanket	f_k	Dimensionless	*	
%Body surface exposed to mattress	f_k	Dimensionless	*	
%Head exposed to blanket	f_k	Dimensionless	*	
%Head exposed to mattress	f_k	Dimensionless	*	
%Head exposed to air	f_a	Dimensionless	*	
Evaporative efficiency of sweat	e	Dimensionless	*	
Relative humidity of expired air	H_a	Dimensionless	*	
Water vapor permeability of blanket	i	Dimensionless	*	
Patient weight	n	kg		†
Metabolic rate	$\dot{M}$	W		†
Excess energy production	$\dot{E}$	W	*	†

* Variables that appear in equations of heat transfer ($\dot{Q}$). † Variables that appear in equations of heat generation ($\dot{M}$).

environment at the rate it is produced, so his body temperature will be expected to rise. This rate of rise is calculated (Ref. 8, p. 5)

$$\text{time (s)} = \frac{3{,}500 n \Delta T}{\dot{E}} \qquad (2)$$

where 3,500 is specific heat of body tissue ($J \cdot °C^{-1} \cdot n^{-1}$), n is weight (kg), and ΔT is incremental change in temperature (°C).

In the analyses performed in this model, the time for the temperature to rise a given amount is calculated in increments of 0.2°C. Reducing these increments to 0.1°C diminished the time for a given temperature rise by 2–4%. The elapsed time necessary for the infant to progress from 41 to 43.4°C is designated as the ET_{41}.

BMR rises with body temperature, a phenomenon known as the Q_{10} effect. The BMR at a given temperature can be calculated by using a modification of the Arrhenius equation (Ref. 8, p. 11)

$$\dot{M}_{T_{sk}} = \dot{M}_{37} a_b 2.29^{\left(\frac{T_{sk}-37}{10}\right)} \qquad (3)$$

where $\dot{M}_{37}$ is BMR at 37°C body temperature (W); a_b is body surface area, BSA (m^2); and T_{sk} is considered equal to core temperature (°C).

The value of Q_{10} used in this calculation is derived from a pooled estimate of the Q_{10} effect (Ref. 8, p. 3). Choosing the proper metabolic rate to use in this model is of prime importance, inasmuch as metabolic heat is the driving force behind the development of hyperthermia. Estimates of the BMR of infants are usually stated in units of caloric use ($cal \cdot kg^{-1} \cdot day^{-1}$) or in units of O_2 consumption ($ml\ O_2 \cdot kg^{-1} \cdot min^{-1}$). When these are converted into units of energy expended (W/m^2), the units used in this model, the estimates of BMR range from 40 (42) to 62 W/m^2 (2).

The influence of age on metabolic rate must also be considered. Investigations show that the metabolic rate rises during the first few months of life until it exceeds 50 W/m^2 (24, 29). By 6 mo of age the metabolic rate has reached the level at which it will remain for the first few years of life (29).

By itself, the BMR does not adequately describe the metabolic heat generated by an infant. Even something as simple as the digestion of a milk meal can elevate an infant's metabolic rate by 10–25% (34). An awake active infant may have a metabolic rate as high as 130 W/m^2 (34). It is well known that minor stress, such as an illness, elevates the metabolic rate well above basal levels.

Because infants are rarely in a state of the lowest metabolic activity (BMR) (40), a metabolic rate of 60–75 W/m^2 is used in this model. This range furnishes a conservative estimate of the normal increases in BMR as the infant grows older and includes increases above BMR that accompany digestion of a meal and that may occur with the stress of a minor febrile illness.

The routes for heat transfer to the environment are radiation, conduction, convection, and evaporation. The detailed equations for these are found in the APPENDIX (*Eqs. A1–A6*). These losses are calculated for each portion of the body and summed to represent the total heat transfer to the environment

$$\dot{Q}_{tot} = \dot{Q}_{rad} + \dot{Q}_{conv} + \dot{Q}_{cond} + \dot{Q}_{e(air)} + \dot{Q}_{e(bla)} + \dot{Q}_{resp} \qquad (4)$$

where $\dot{Q}_{rad}$ is radiative heat loss (W), $\dot{Q}_{conv}$ is convective heat loss (W), $\dot{Q}_{cond}$ is conductive heat loss (W), $\dot{Q}_{e(air)}$ is evaporative heat loss from skin exposed to air (W), $\dot{Q}_{e(bla)}$ is evaporative heat loss from skin covered by insulation permeable to water vapor (W), and $\dot{Q}_{resp}$ is respiratory heat loss (W).

The infant's body surface is mathematically represented as two cylinders. Nineteen percent of the BSA is assigned to the smaller cylinder, which represents the head (7). The balance of the BSA is assigned to the larger cylinder, which represents the body of an infant sleeping with his extremities clasped against his torso. In this model, the torso is always covered with a blanket. A variable portion of the head is covered with the blanket. The BSA exposed to the air (f_a) is calculated from

$$f_a = \frac{\text{BSA} \cdot 0.19 \cdot \%\text{head exposed to air}}{100} \qquad (5)$$

The routes of heat loss for the area under the blanket are conductive and evaporative losses across a blanket. Conductive losses are also calculated for the mattress. Most infant mattresses are covered with a plastic sheet, so no evaporative losses are calculated for the mattress. For the area outside the blanket (i.e., the head), the routes of heat loss are convective, radiative, and evaporative losses to the air and conductive losses across the mattress. Respiratory evaporative heat loss is calculated, with allowance for the increased metabolic and respiratory rates as temperature increases. The increase of water vapor pressure with rising temperature is consid-

TABLE 2. *Equations used to describe heat loss from body surface*

Route of Heat Loss	Mechanism of Heat Loss					
				Evaporation		
	Convection	Conduction	Radiation	Respiratory	Skin	Blanket
Across blanket		Limbs, torso, part of head (f_k) (*Eq. A3*)				
Across mattress		Limbs, torso, part of head (f_k) (*Eq. A3*)				
Into air	Exposed portion of head (f_a) (*Eq. A2*)		Exposed portion of head (f_a) (*Eq. A1*)	Respiratory tract (*Eq. A6*)	Exposed portion of head (f_a) (*Eq. A4*)	Limbs, torso, part of head (f_k) (*Eq. A5*)

ered in equations of evaporative heat loss. Room temperature and humidity are incorporated into equations of heat loss. To mimic maximum heat loss, skin temperature is regarded as equal to core temperature and the skin is regarded as entirely wet with sweat.

Heat liberated by metabolism is compared with heat loss. If heat loss exceeds heat production ($\dot{E} < 0$), the infant is not thermally entrapped and may thermoregulate normally. If heat production is greater than maximum heat loss ($\dot{E} > 0$), the infant is thermally entrapped and the time to progress to 43.4°C is calculated. The rate of rise in body temperature is calculated from the specific heat of body tissue (Ref. 8, p. 3) and the excess heat (in W) produced by the thermally entrapped infant.

In the model, each equation may be used more than once to describe heat transfer from different body sites. For example, the equation for conductive heat transfer is used twice: *1*) to describe heat transfer across the blanket and *2*) to describe heat transfer across the mattress. In the two applications of this equation, the thermal conductivity constant (τ) and the BSA (f_k) are different, although their symbols are identical. There is an f_k and a τ for conduction across the blanket. There is a different f_k and τ for conduction across the mattress. The use of different values for variables represented by the same symbol is necessary to present general equations for heat transfer. In this manner, it is possible to avoid presenting a larger group of equations, many of which would be redundant. In total, 16 variables (Table 1) can be altered to observe the effect on excess energy production ($\dot{E}$). Within the model, these variables can be manipulated independently. Table 2 shows the routes of heat loss and the equations used to quantify the heat loss.

The atmospheric temperature (T_a) may be varied over an unlimited range. Ambient water vapor pressure ($P_{w,a}$) may be varied from 0 to atmospheric saturation (0–100% relative humidity). For ease of calculation, blanket thickness and mattress thickness (both designated by b) are represented in meters. The thickness of each of these may be varied separately over an unlimited range. The blanket thermal conductivity constant and mattress thermal conductivity constant are both designated by τ. This variable, a measure of the insulating quality of these materials, may be varied separately for the blanket and the mattress over an unlimited range. The value for τ used in the simulations in this model (0.04) is typical for thick fabrics (Ref. 8, p. 112). This value is used for the blanket and mattress. The a_b is determined from n by use of the following formula (4)

$$a_b = 0.1 \cdot n^{0.666} \quad (6)$$

The portion of the body surface (f_k) exposed to the blanket and to the mattress may be varied. The portion of the head exposed to the blanket and to the mattress is represented by the variable f_k. Changes in one f_k variable necessarily led to reciprocal changes in another f_k variable (e.g., if the portion of the head exposed to air is increased, the portion of the head exposed to the blanket or mattress must be reduced). Conductive losses are calculated for all f_k variables. Evaporative losses across the blanket are also calculated for the appropriate proportion of f_k variables. The water vapor permeability of the blanket (i) is a measure of how readily water vapor traverses an insulating material and may be varied from 0 to 1. An i of 0.3 is used in the simulations in this model. This value is between that of a permeable coat (19) and light khaki fabric (52). Because most infant mattresses are covered with plastic, evaporative losses across the mattress are treated as nonexistent.

The portion of the head exposed to the air is represented by the variable f_a. Convective, radiative, and evaporative heat losses are calculated for this portion of the BSA. Respiratory heat loss depends almost completely on the relative humidity of exhaled air (H_a) (16); a typical value is 0.8 (33); n and metabolic rate ($\dot{M}$) may also be altered within the model.

The evaporative efficiency of sweat (e) is a measure of how efficiently sweat removes heat from a complex shape like the human body (26). Ambient air may not circulate well to certain regions of the body (e.g., the inner thigh), reducing evaporative losses from these regions compared with evaporative losses from a flat surface. A typical value for e is $\leq$0.4 (26). In the model, this value may be varied from 0 to 1.

It is possible to gauge the relative effects of these variables on the risk of thermal entrapment. If 15 of the 16 variables are held constant and one variable is manipulated, the effect of the manipulated variable on the risk of thermal entrapment can be explored. If the infant is thermally entrapped, the model indicates ET_{41}. These two temperatures are chosen because 41°C is close to the upper limit of normally occurring febrile temperatures (46) and 43°C is rapidly lethal (21).

To illustrate the operation of the model, the details of

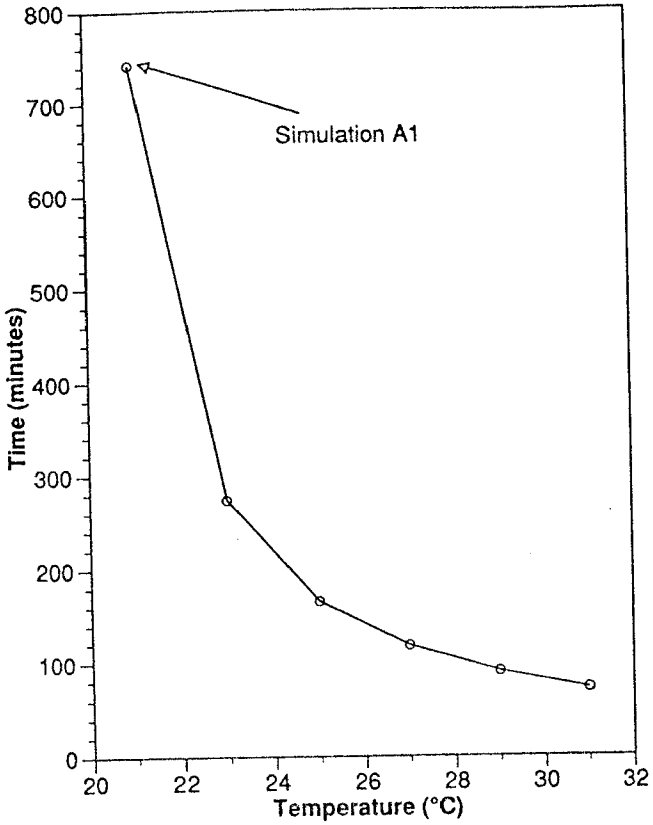

FIG. 1. Effect of increasing room temperature on time for a thermally entrapped infant to progress from 41 to 43.4°C (ET_{41}). Conditions are identical to *simulation A1* except for varying temperature. At 21°C, all conditions are identical to *A1*.

two different sets of simulations are explored (*A* and *B* simulations). The most important difference between these simulations is that less of the BSA is exposed to air in *A* than in *B* simulations. In a different group of analyses, the effect of altering selected variables in the model (room temperature, relative humidity, exposed BSA, and blanket thickness) is explored in greater detail (Figs. 1–4).

RESULTS

In most situations, the mechanisms of cutaneous vasodilation and sweating transfer enough heat to the environment to prevent overheating. Nevertheless, in some circumstances, the model indicates that it is possible for a normal infant to be thermally entrapped.

In Table 3 *A1–A6* show the effects caused by changes to five of the conditions in *simulation A0*. Four of these conditions (atmospheric temperature, relative humidity, blanket thickness, and metabolic rate) are increased 20% above the starting values. The fifth variable (the quantity of head exposed to the air) is increased by 10% above its starting value. The infant is not thermally entrapped in the conditions in *simulation A0* ($ET_{41} = \infty$). Each of the changes in *A1–A6* causes thermal entrapment, as indicated by the ET_{41}. When several of these changes occur together (*A4–A6*), the ET_{41} is further shortened.

The magnitude of change in the ET_{41} produced by a 5% change in a single variable depends on the state of the other heat exchange variables. Table 4 shows the effect of a 5% change in the 16 variables in the ET_{41} of *simulations A1–A6* (Table 3). The starting point for each of the columns (baseline ET_{41}) is the ET_{41} from *simulations A1–A6*. The change in ET_{41} from baseline values ($\%ET_{41}$) permits comparison of the magnitude of the effect produced by alteration of the variables. In each simulation, reduction of the exposed skin of the head causes the greatest reduction in ET_{41}. For example, in *simulation A1*, a 5% reduction in the portion of the head exposed to the air shrinks the ET_{41} to 35% of its starting value. Also in *simulation A1*, increasing the portion of the head exposed to air (reducing the portion exposed to the blanket) by 5% slows warming, increasing the ET_{41} to 118% of baseline value. It is noteworthy that the effect of increased blanket thickness is always less than that caused by reducing the portion of the head exposed to the air.

In the model, the portion of the body exposed to the blanket can be increased by reducing the portion of the body exposed to the mattress. This makes it possible to compare the effect of different sleeping positions (e.g., if sleeping on the side is compared with sleeping on the back, the lateral position exposes more of the body to the blanket and less to the mattress). Increasing the portion of the body exposed to the blanket prolongs the ET_{41} by 361% in *simulation A1*. This manipulation increases evaporative heat transfer, because a smaller portion of the body is exposed to the mattress (there is no evaporative heat transfer across the mattress). The effect of this change on the ET_{41} is smaller in *simulations A2–A6*.

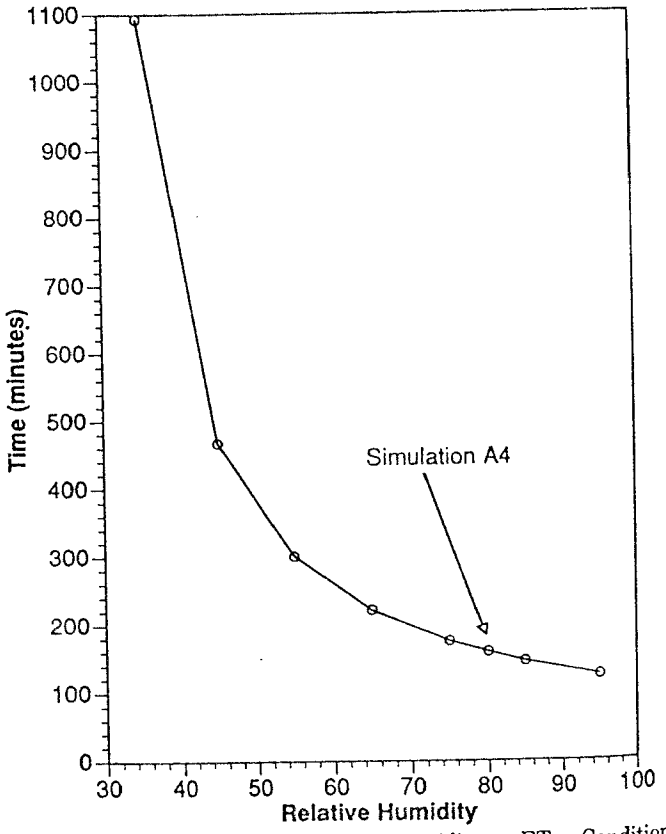

FIG. 2. Effect of increasing relative humidity on ET_{41}. Conditions are identical to *simulation A4* except for varying humidity. At 80% relative humidity, all conditions are identical to *A4*.

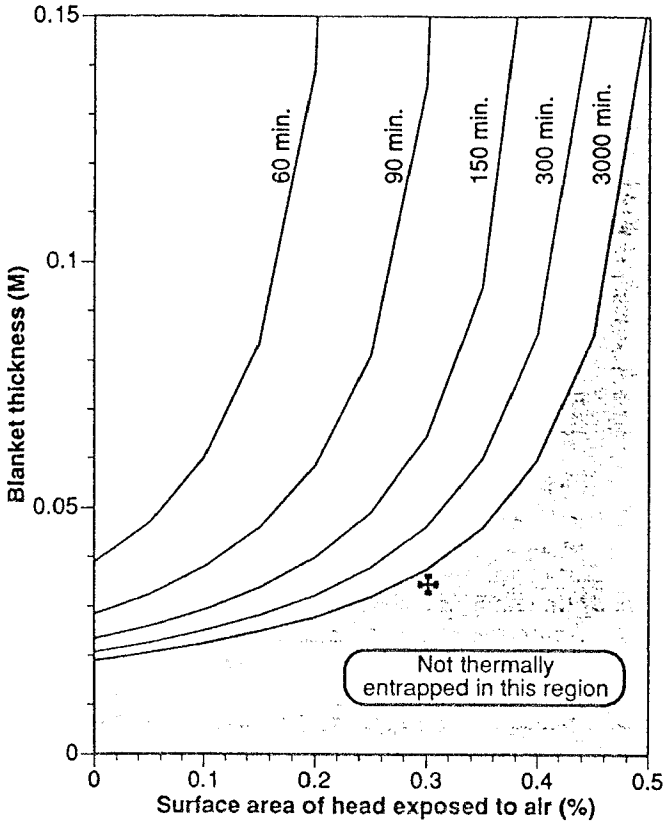

FIG. 3. Influence of blanket thickness and exposed surface area of the head on ET_{41} and thermal entrapment. Conditions for this simulation are identical to *A0* except for altering blanket thickness and exposed surface area of the head. All conditions are identical to *simulation A0* at ✣. Lines indicate conditions necessary to produce a given ET_{41}.

The model quantifies heat transfer (in W) to the environment at all body temperatures from 37 to 43.4°C. The quantity of heat transferred at a given body temperature depends on the 16 variables. For the conditions stipulated in *simulations A0–A6* (Table 3), the quantity of heat transferred to the environment at a body temperature of 41°C is shown in Table 5. This allows comparison of the magnitude of heat lost via each route. The avenues of greatest heat loss are evaporative transfer across the blanket and evaporative transfer from the head. Evaporative heat loss across the blanket exceeds conductive heat loss across the blanket in all these simulations. Even though exposed surface area of the head is 5.7% of the total BSA, the heat lost through this route exceeds heat loss from the balance of the body surface in all except *simulation A6,* in which the exposed surface area of the head has been reduced to 3.8% of the BSA. At this point, heat loss from the portion of the body that is under the blanket (96.2% of the BSA) exceeds heat loss from the head.

For all the simulations except *A3,* the metabolic rate is 25.46 W (in *simulation A3,* the metabolic rate is 30.55). If the infant is to avoid thermal entrapment, total heat loss must exceed heat produced by the metabolic rate. This requirement is met only in the conditions in *simulation A0.* In *simulations A1–A6,* heat production exceeds heat loss, resulting in thermal entrapment (Table 5). If the discrepancy between heat production and heat loss grows larger, the infant's body temperature rises more rapidly and the ET_{41} becomes shorter.

In all the *B* simulations 70% of the head is exposed to air, whereas in the *A* simulations 30% of the head is exposed to the air (only 20% of the head is exposed to the air in *A6*). In Table 3 *B1–B4* show large changes in a few of the variables that affect heat loss (atmospheric temperature, relative humidity, and blanket thickness). In contrast to the *A* simulations, in which small changes in relative humidity or atmospheric temperature led to thermal entrapment, in the *B* simulations, much larger changes in these parameters do not cause thermal entrapment. In *simulation B3,* the blanket thickness is increased to 1 m (a situation that would never be encountered in reality), effectively eliminating heat transfer across the blanket. Despite this unusual situation, the infant is still not thermally entrapped. In *simulation B4,* the combination of 100% relative humidity and a blanket thickness of 1 m is also insufficient to cause thermal entrapment.

For the conditions stipulated in *B0–B4,* the quantity of heat transferred to the environment at a body temperature of 41°C is shown in Table 6. This allows comparison of the magnitude of heat lost via each route. In each simulation, the heat lost exceeds the infant's metabolic rate (25.46 W at 41°C), so the infant is not thermally entrapped. Compared with the *A* simulations, the most notable difference is that more heat is lost from the head. In

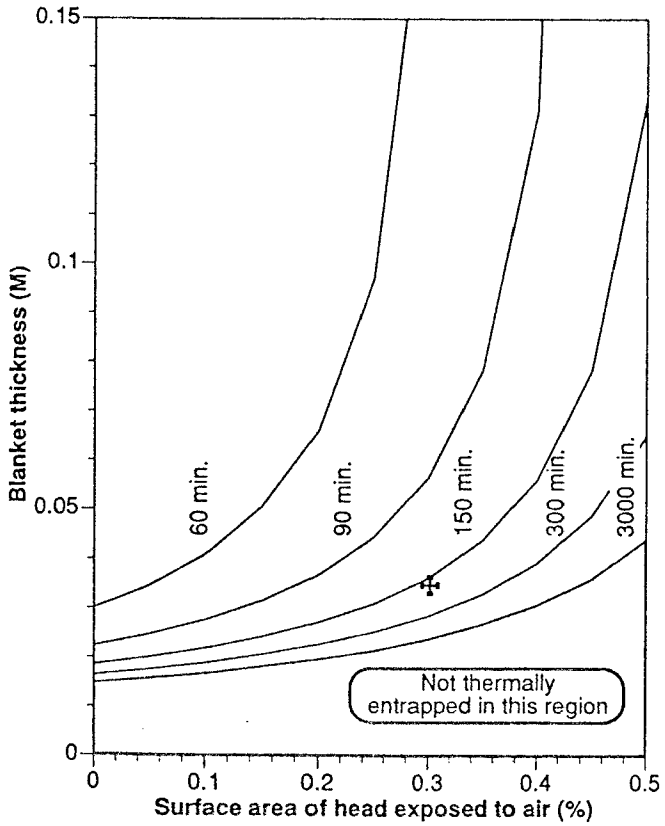

FIG. 4. Influence of blanket thickness and exposed surface area of the head on ET_{41} and thermal entrapment. Conditions for this simulation are identical to *A4* except for altering blanket thickness and exposed surface area of the head. All conditions are identical to *simulation A4* at ✣. Lines indicating conditions necessary to produce a given ET_{41} are shifted to right compared with Fig. 3.

TABLE 3. *Variables in simulations A and B*

Variable	A Simulations							B Simulations				
	A0	*A1*	*A2*	*A3*	*A4*	*A5*	*A6*	*B0*	*B1*	*B2*	*B3*	*B4*
T_a, °C	21	21	**25.2**	21	**25.2**	**25.2**	**25.2**	21	**31**	21	21	21
Relative humidity, %	60	**80**	60	60	**80**	**80**	60	60	60	**100**	60	**100**
b, m												
Blanket	0.035	0.035	0.035	0.035	0.035	**0.042**	**0.042**	0.035	0.035	0.035	0.035	0.035
Mattress	0.012	0.012	0.012	0.012	0.012	0.012	0.012	0.012	0.012	0.012	0.012	**1.0**
τ, $W \cdot m^{-1} \cdot °C^{-1}$												
Blanket	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04
Mattress	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04
BSA, m^2	0.29	0.29	0.29	0.29	0.29	0.29	0.29	0.29	0.29	0.29	0.29	0.29
%Body surface exposed to blanket	70	70	70	70	70	70	70	**0**	**0**	**0**	**0**	**0**
%Body surface exposed to mattress	30	30	30	30	30	30	30	30	30	30	30	30
%Head exposed to blanket	40	40	40	40	40	40	**50**	40	40	40	40	40
%Head exposed to mattress	30	30	30	30	30	30	30	30	30	30	30	30
%Head exposed to air	30	30	30	30	30	30	**20**	**70**	**70**	**70**	**70**	**70**
M, W/m^2	62	62	62	**74**	62	62	62	62	62	62	62	62
e	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
i	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
n, kg	5	5	5	5	5	5	5	5	5	5	5	5
H_s, %	80	80	80	80	80	80	80	80	80	80	80	80
ET_{41}	∞	742	256	163	160	119	92	∞	∞	∞	∞	∞

ET_{41}, elapsed time necessary for progression from 41 to 43°C; other abbreviations as in Table 1. In *simulation A0* and in all *B* simulations, infant is not thermally entrapped ($ET_{41} = \infty$). All values except those in boldface are identical to values for *simulation A0*.

all the *B* simulations, sufficient heat is lost from the exposed skin of the head to prevent thermal entrapment under conditions that would have resulted in thermal entrapment in the *A* simulations.

The model shows that the time to progress to lethal hyperthermia may be quite long in some situations and <90 min in others. The rate of warming of a thermally entrapped infant is an accelerating function: the warmer the infant, the more rapidly he warms. As body temperature rises, heat production grows more rapidly than heat loss. The thermally entrapped infant will progress more rapidly from 41 to 42°C than from 37 to 38°C.

Manipulation of a single variable, while the others are held constant, shows that as heat loss is prevented, one of two conditions commonly results: *1*) The infant is not thermally entrapped, even at extreme values of the ma-

TABLE 4. *Effect of ±5% change in model variables on ET_{41}*

Variable	% Change	Simulation					
		A1	*A2*	*A3*	*A4*	*A5*	*A6*
Baseline ET_{41}		742	256	163	160	119	92
T_a	+5	391 (53)	190 (74)	139 (85)	128 (80)	102 (85)	84 (91)
Relative humidity	+5	548 (74)	223 (87)	152 (93)	146 (91)	112 (94)	89 (96)
b							
Blanket	+5	481 (65)	219 (86)	146 (89)	146 (91)	113 (94)	88 (95)
Mattress	+5	720 (97)	254 (99)	163 (99)	159 (100)	119 (100)	93 (100)
τ							
Blanket	+5	473 (64)	218 (85)	145 (89)	145 (91)	112 (94)	88 (95)
Mattress	+5	719 (97)	254 (99)	162 (99)	159 (99)	119 (100)	93 (100)
%Body surface exposed to blanket	+5	2,676 (361)	320 (125)	191 (117)	181 (113)	128 (107)	99 (106)
%Body surface exposed to mattress	+5	455 (61)	214 (83)	143 (88)	144 (90)	112 (93)	88 (94)
%Head exposed to blanket	+5	876 (118)	269 (105)	169 (103)	165 (103)	121 (102)	94 (101)
%Head exposed to mattress	+5	645 (87)	245 (96)	158 (97)	156 (97)	117 (98)	92 (99)
%Head exposed to air	−5	260 (35)	162 (63)	115 (70)	120 (75)	95 (80)	77 (82)
M	+5	329 (44)	180 (70)	124 (76)	126 (79)	99 (83)	81 (87)
e	−5	555 (75)	230 (90)	152 (93)	151 (94)	114 (95)	90 (97)
i	−5	554 (75)	230 (90)	152 (93)	151 (94)	115 (96)	90 (97)
n	+5	754 (102)	260 (102)	166 (102)	163 (102)	121 (102)	94 (102)
H_s	−5	606 (82)	238 (93)	155 (95)	153 (95)	115 (97)	90 (97)

Values in parentheses represent % change from baseline ET_{41}.

TABLE 5. *Heat lost at 41°C in A simulations*

Route of Heat Loss	Simulation						
	A0	*A1*	*A2*	*A3*	*A4*	*A5*	*A6*
Conduction, blanket	4.30	4.30	3.39	4.30	3.39	2.83	2.91
Conduction, mattress	0.58	0.58	0.46	0.58	0.46	0.46	0.46
Evaporation, blanket	6.67	6.14	6.22	6.67	5.53	4.61	5.34
Evaporation, head	6.64	6.11	6.18	6.64	5.50	5.50	4.12
Radiation, head	2.07	2.07	1.67	2.07	1.67	1.67	1.11
Convection, head	3.13	3.13	2.48	3.13	2.48	2.48	1.65
Evaporation, respiratory	2.75	2.47	2.51	3.30	2.15	2.15	2.51
Total heat loss	26.15	24.81	22.92	26.70	21.19	19.70	18.11

Values represent quantity of heat (in W) lost at 41°C. Total heat loss in all simulations except *A3* must exceed 25.46 W to avoid thermal entrapment. In *simulation A3,* total heat loss must exceed 30.39 W to avoid thermal entrapment, because metabolic rate is higher than in the other simulations.

nipulated variable, because the nonmanipulated variables permit enough heat loss to allow thermal homeostasis. 2) As the manipulated variable is changed to prevent heat loss, the infant is thermally entrapped and the time to progress to lethal hyperthermia asymptotically approaches a maximum rate (Figs. 1 and 2). This maximum rate is different for each set of variables. Whether the manipulated variable sufficiently hampers heat loss to cause thermal entrapment depends on the state of the nonmanipulated variables. If the whole system favors heat loss, thermal entrapment may be impossible.

Figures 3 and 4 illustrate the effect of altering exposed BSA and blanket thickness on thermal entrapment. The conditions in Fig. 3, except for varying the blanket thickness and exposed BSA, are identical to those in *simulation A0* (the exact conditions in *A0* occur at the ⊕). Likewise, the conditions in Fig. 4, except for varying blanket thickness and exposed BSA, are identical to those in *simulation A4* (the exact conditions in *A4* occur at the ⊕). *Simulations A0* and *A4* fall on identical points in both graphs, because they have identical blanket thickness and exposed BSA. In Fig. 3, this point falls in a region where the simulated infant would not be thermally entrapped. In Fig. 4, other environmental conditions (warmer atmospheric temperature and higher humidity) cause this point to fall in a region where the simulated infant is thermally entrapped. The effect of these environmental conditions is to shift the curves for the ET_{41} to the right, lessening the blanket thickness needed to cause thermal entrapment.

TABLE 6. *Heat lost at 41°C in B simulations*

Route of Heat Loss	Simulation				
	B0	*B1*	*B2*	*B3*	*B4*
Conduction, blanket	3.79	1.71	3.79	0.13	0.13
Conduction, mattress	0.58	0.26	0.58	0.58	0.58
Evaporation, blanket	5.88	4.62	4.94	0.21	0.17
Evaporation, head	15.48	12.15	13.01	15.48	13.01
Radiation, head	4.84	2.30	4.84	4.84	4.84
Convection, head	7.31	3.29	7.31	7.31	7.31
Evaporation, respiratory	2.75	1.99	2.19	2.75	2.19
Total heat loss	40.64	26.31	36.67	31.31	28.24

Values represent quantity of heat (in W) lost at 41°C. Total heat loss must exceed 25.46 W to avoid thermal entrapment.

DISCUSSION

Unlike adult hyperthermia, which generally has an obvious antecedent such as excessive exertion in hot weather (9, 54), infant hyperthermia may occur under circumstances that appear ordinary. The results of this model show that *1)* thermal entrapment is possible under a variety of circumstances, *2)* progression to lethal hyperthermia may happen rapidly, and *3)* the environmental circumstances causing thermal entrapment might not be easily recognized.

Pathophysiology of hyperthermia. Hyperthermia and fever are different physiological processes that lead to elevation of body temperature by different mechanisms. During fever, the hypothalamic thermoregulatory center is "reset" by the effect of interleukin-1. Body temperature is elevated by augmentation of heat production (chills or shivering) and by restriction of heat loss through vasoconstriction and cessation of sweating (12, 15, 45). The body opposes peripheral cooling by increasing heat production and more vigorous vasoconstriction. Only when the blood bathing the hypothalamus has reached the desired temperature are the usual thermoregulatory mechanisms invoked to maintain thermal homeostasis at the febrile temperature. The temperature does not fall until the effect of interleukin-1 has abated. This process is governed by precise neurophysiological control and rarely results in temperatures >41.1°C (13, 31).

In contrast, hyperthermia is caused by heat storage in excess of heat loss without a change in temperature control (30). Temperature rise is produced by an inability to disperse heat despite vasodilation and sweating. Unlike the febrile state, if peripheral cooling should occur, it is not opposed and causes the body temperature to fall. In the hyperthermic state, unlike the febrile state, the temperature rises because heat production overwhelms heat loss mechanisms. As shown by this model, lethal temperature elevation may result.

Heat loss may be increased by changing the local environment: removing insulation (clothing), increasing airflow, seeking a cooler location, or other behavioral measures. Adults are able to regulate their local environ-

ment, allowing them to adapt to extreme temperatures without disruption of thermal homeostasis. Unfortunately, an infant has no control over his local environment. He is unable to remove his clothes or even his blankets in response to thermal stress. Loss of this important thermoregulatory mechanism places him at increased risk of hyperthermia, even in some situations that may not appear dangerous. The one measure of environmental control allotted to the infant is the ability to cry so he may alert his parents to a potentially dangerous situation. Surprisingly, there is evidence that some infants are not aroused despite rapidly rising rectal temperatures (40).

The infant also has the added thermal risks of a BMR that is approximately twice that of the adult (2, 25) and immature sweat-producing capabilities (17, 18, 23). Human infants also produce heat through norepinephrine-mediated stimulation of brown fat (42). Paradoxically, norepinephrine released during hyperthermic stress may exacerbate heat production. These unique developmental and physiological characteristics increase the infant's risk of hyperthermia.

A thermally entrapped infant's rate of temperature rise depends on the rate of heat accumulation. If the infant's body temperature is barely above the point at which thermal entrapment occurs, the infant's temperature will rise extremely slowly, because heat production barely exceeds maximum heat loss. On the other hand, if enough heat loss is prevented, heat accumulation will proceed rapidly, causing his body temperature to rise quickly.

Because thermal entrapment and fever are different processes, they can occur separately or together. If they occur together, the rate of temperature rise is accelerated. When an infant is both febrile and thermally entrapped, he will conserve heat (vasoconstriction and cessation of sweating) and increase heat production (shivering or chills) until his core temperature exceeds the febrile set point of the anterior hypothalamus. The insulation surrounding the infant will speed this process by reducing heat transfer to the environment. In this way, the processes of fever and thermal entrapment act in a complementary manner to produce a brisk rise in temperature.

When the febrile "goal" temperature is achieved, the infant will undergo cutaneous vasodilation and will begin to sweat in an attempt to maintain the goal temperature. If the infant has been shivering (chills) and if norepinephrine release has caused increased thermogenesis from brown fat, these processes will cease. Unfortunately, the BMR of this excessively insulated infant is sufficient to drive his temperature upward. As heat accumulates, the BMR will rise, as dictated by the Q_{10} effect (*Eq. 3*). The infant's temperature will continue upward until the cycle is interrupted by death or until sufficient insulation is removed from the infant.

Compared with thermal entrapment alone, the processes of fever and thermal entrapment increase the rate of temperature rise from the afebrile state to the febrile goal temperature. The rate of temperature rise above this point is determined by factors governing thermal entrapment. The overall effect is to shorten the time to progress from an afebrile temperature to lethal hyperthermia.

Although it would be desirable for a thermally entrapped infant to abort a febrile response, there is no evidence that the feedback systems of temperature control have this capability. Once the anterior hypothalamus has been stimulated by interleukin-1, the body responds by rapidly elevating its temperature, no matter how severely the local environment may restrict heat loss.

The thickness of the blankets used in these simulations (3.5 cm) may seem excessive; however, this may not be at variance with the clothing practices of some parents. In one survey of infant clothing practices, 5% of the babies were visibly sweating, and 25% of the infants were heavily dressed (37). There was no correlation between the room temperature and the quantity of clothing on the infant (some heavily dressed infants were housed in warm rooms). The investigators believed that one-third of the infants were excessively insulated for the environmental conditions. In another study, 2.5% of infants were covered with blankets $\geq$2.66 cm thick (35). The average thickness of clothing covering the chest of the infants in this study was an additional 0.59 cm (total thickness $\geq$3.25 cm). These authors also found no correlation between room temperature and insulation placed over the infant. In neither of these investigations (35, 37) was an attempt made to quantitate the insulating properties of infant diapers. The additional thickness of the diapers and the vapor barrier surrounding the diaper would reduce heat transfer to the environment. There is also evidence that the quantity of insulation placed on an infant may be greater when the infant is ill. Over 20% of mothers stated that they would warm an infant with a cold and a high temperature (14). These data indicate that a small proportion of infants are as well insulated as the simulated infant in the mathematical model.

One might suppose that a visual inspection would quickly determine whether an infant is thermally entrapped. This does not appear always to be the case. Our daily experience leads us to believe that blanket thickness is the most important variable in regulating heat loss. In contrast, the model shows that exposed BSA is the major determinant of heat loss when an infant is facing thermal entrapment. These different perspectives are easily reconciled when one considers the important differences between an adult using a blanket to keep warm and a thermally entrapped infant that needs to lose heat.

The state of the skin is very different, depending on whether one needs to conserve or lose heat. When it is necessary to conserve heat, the skin is cool and dry. Under these conditions, conductive losses across the blanket are especially important. In contrast, when it is necessary to transfer heat to the environment, the skin is warm and wet. These circumstances greatly increase heat loss from exposed skin (especially evaporative losses).

A person sleeping in a cool room reduces exposed body surface to a minimum, diminishing radiative and convective heat loss. Evaporative heat loss is reduced to a minimum (sweating ceases in cool environments). This

means that conductive heat loss across the blanket is the major route for heat transfer to the environment. Under these circumstances, the most effective way to reduce heat loss is to increase the thickness of the blanket. The amount of heat conducted to the blanket surface is inversely proportional to the blanket thickness (*Eq. A3*). A person seeking to become comfortable in a cool environment easily appreciates that blanket thickness is a prime determinant of heat loss. We develop an intuitive feeling about the importance of blanket thickness in reducing heat loss in a cool environment. The model shows that this intuitive understanding may be misleading when one attempts to estimate the risk of thermal entrapment.

When an infant is thermally entrapped, he maximizes heat transfer to the environment by cutaneous vasodilation and sweating. In *simulations A1–A4*, a blanket 3.5 cm thick inhibits heat loss so effectively that the heat loss from the exposed surface of the head (6% of the total body surface) is greater than that from the rest of the body surface.

Figures 3 and 4 attest to the importance of knowing the exact extent of the exposed BSA in assessing the risk of thermal entrapment. Small differences in exposed BSA may be pivotal in determining the risk of thermal entrapment. Figures 3 and 4 indicate that exceptionally thick blankets cannot cause thermal entrapment unless a sufficient portion of the head is covered. Figure 4 shows that if <30% of the head is exposed to the air, a substantial risk of lethal hyperthermia is posed by only 3 cm of blanket thickness. In contrast, because a cooler less humid environment is modeled in Fig. 3, thicker blankets would be needed to cause thermal entrapment.

Additional evidence that exposed surface area is of paramount importance in heat transfer is presented in Table 6. In these examples, more of the head is uncovered, so the exposed skin of the head comprises 13% of the total BSA. Through this portal, heat is transferred to the environment so successfully that thermal entrapment is impossible under certain extreme conditions of temperature, humidity, or blanket thickness.

The complex interaction of multiple variables makes it nearly impossible to evaluate the risk of thermal entrapment by a visual inspection of the infant's environment. The most important variable is the quantity of exposed skin. If the entire head and neck are exposed, thermal entrapment is impossible, except under the most extreme circumstances. In contrast, if the head is partially covered, thermal entrapment may happen under very unremarkable circumstances. The intricacy of these interactions may make it difficult for physicians to establish hyperthermia as a cause of infant injury.

Implications. The model predicts that one should find heat-related injury and mortality among infants. There is some clinical evidence that hyperthermia may be a cause of morbidity and mortality. Some authors have suggested that hyperthermia may be the cause of hemorrhagic shock and encephalopathy syndrome (HSE) (6, 43, 50, 51). Others have suggested that a small number of deaths presently attributed to sudden infant death syndrome (SIDS) may be caused by hyperthermia (1, 3, 36, 44, 47). Unfortunately, the pathological (11, 32, 38) and biochemical (5, 10, 28, 48) changes seen after known heat injury are nonspecific. This hampers the ability of an investigator to retrospectively establish hyperthermia as the cause of an illness or death.

This model is useful in illustrating how it may be possible for an infant to sustain injuriously high temperatures. The model also shows how life-threatening hyperthermia may occur during the time that an infant may spend asleep, unobserved by his parents. This is a requisite if hyperthermia is to be considered a possible mechanism for HSE or some deaths incorrectly attributed to SIDS. Investigators studying the role of hyperthermia in these illnesses may be frustrated by the paucity of environmental circumstances suggesting a high risk of hyperthermia. The model shows that hyperthermia may occur rapidly in a febrile infant in circumstances that appear normal on visual inspection. When confronted with the distress of finding a severely ill or dead infant, few parents will be able to accurately recall the exact placement and quantity of blankets and other insulation. Consequently, the essential clue to thermal entrapment, the quantity of BSA exposed to the air, will usually be unknown.

Attempts to measure the temperature of infants to establish hyperthermia as a mechanism of illness may not be informative, inasmuch as the temperature of uncovered infants declines rapidly. When an infant reaches medical attention, his temperature may have declined to an normal level. Effective assessment of the role of hyperthermia in these illnesses may await the development of dependable biochemical or pathological markers of hyperthermic injury.

Hyperthermia cannot account for cases of SIDS that are alleged to have occurred within a few minutes after an infant was put to bed by a parent. There is a maximum rate of warming for a given metabolic rate. This maximum rate occurs if little or no heat is transferred to the environment. In this setting, all the energy liberated by metabolism serves to warm body tissue. The rate of warming is determined by the metabolic rate and the specific heat of body tissue. If it were possible to prevent all heat loss, ET_{41} would be ~25–30 min, depending on the metabolic rate. The model indicates that, under realistic environmental conditions, lethal hyperthermia is unlikely to occur in <60–90 min. Depending on the conditions, the time may be substantially longer than this but still within the time an infant could be asleep unobserved (see Figs. 1 and 2).

Summary. This mathematical model shows that the temperature of a febrile thermally entrapped infant may rise rapidly enough for lethal injury to occur during the time that the infant was presumed to be sleeping. The crucial events in an episode of severe hyperthermia are *1)* reduction in the exposed (uncovered) BSA below a critical minimum for a given situation and *2)* development of a febrile response to an infection. The infection serves as a stimulus for the body to produce a febrile response, accelerating the accumulation of heat by the thermally entrapped infant. The quantity of blankets over the infant may not appear excessive, because the exposed BSA is usually more important in determining thermal entrapment than is blanket thickness.

Although well-documented cases of hyperthermic in-

jury and death in infants are uncommon, hyperthermia has been suggested as the cause for HSE and for a small number of deaths erroneously classified as SIDS. This model of hyperthermic injury is consistent with these hypotheses and illustrates how it may be possible for a normal infant to suffer injurious or lethal hyperthermia. Further investigation of the role of hyperthermia in these illnesses may be warranted.

APPENDIX

Calculations and Assumptions Used in Creating This Computer Model

Radiation.

$$\dot{Q}_{rad} = \sigma \epsilon a_b f_a (T_{sk}^4 - T_a^4) \qquad (A1)$$

where σ is the Steman-Boltzman constant [$(5.7 \cdot 10^{-8} \cdot W) \cdot (m^{-2} \cdot °K^{-4})$], ϵ is emittance of the body surface (typical value 0.97), and T_{sk} and T_a are in °K (Ref. 41, p. 146).

Convection.

$$\dot{Q}_{conv} = h_c a_b f_a (T_{sk} - T_a) \qquad (A2)$$

where h_c is convective heat transfer coefficient [typical value 9.4, in $W \cdot (m^{-2} \cdot °C^{-1})$] (Ref. 41, p. 145; value for h_c from Ref. 8, p. 237).

Conduction.

$$\dot{Q}_{cond} = \frac{\tau a_b f_k (T_{sk} - T_a)}{b} \qquad (A3)$$

where τ is mattress and blanket thermal conductivity constant, f_k is used to describe the BSA exposed to the blanket and mattress, and b is thickness of insulating material (m) and is used for mattress and blanket thickness. *Equation A3* appears twice in the model. It is used to describe heat transfer across the mattress and heat transfer across the blanket (*Eq. A3* modified from Ref. 8, p. 112; values for k from Ref. 8, p. 112 and Ref. 49, p. E5).

Evaporation from exposed skin.

$$\dot{Q}_{e(air)} = h_e a_b f_a e (P_{w,sk} - P_{w,a}) \qquad (A4)$$

where $\dot{Q}_{e(air)}$ is evaporative heat loss from skin exposed to air (W), h_e is evaporative heat transfer coefficient [value 21.15, in $W \cdot (Torr^{-1} \cdot m^{-2})$], and $P_{w,sk}$ is vapor pressure of saturated air at T_{sk} (Torr; see *Eq. A7*) [*Eq. A4* modified from Ref. 26, p. 167; values for h_e from Ref. 26, p. 167 (h_e is $2.25 \times h_c$); value for e from Ref. 26, p. 168; value for $h_c = 9.4$ from Ref. 8, p. 237].

Evaporation from covered skin.

$$\dot{Q}_{e(bla)} = \frac{\psi a_b f_k i \tau (P_{w,sk} - P_{w,a})}{b} \qquad (A5)$$

where $\dot{Q}_{e(bla)}$ is evaporative heat loss from skin covered by insulation permeable to water vapor and ψ is a constant (2.2°C/Torr) [*Eq. A5* is modified from Ref. 19, p. 43; variable I (insulation) has been replaced by b/τ to be consistent with other equations in this investigation, constant 16.5 has been replaced by 2.2, because units of vapor pressure in Ref. 19 are kPa, whereas those in this investigation are Torr; some values for i are listed in Ref. 19, p. 54].

Respiratory heat loss.

$$\dot{Q}_{resp} = \eta \beta \dot{M}_{T_{sk}} \alpha \left(\frac{H_s P_{w,sk}}{760\ Torr - H_s P_{w,sk}} - \frac{P_{w,a}}{760\ Torr - P_{w,a}} \right) \qquad (A6)$$

where η is heat of vaporization of water at 35°C ($2.406 \cdot 10^6$ J/kgH2O), β is mass ventilation of air per joule of BMR expended ($1.434 \cdot 10^6$ kg air/J), and α is relative weight of molar quantities of water and dry air (0.622 kgH_2O/kg air) (modified from Ref. 16, p. 29; value for H_s from Ref. 33).

Water vapor pressure at T_{sk}.

$$\log_{10} P_{w,sk} = \frac{-2270.5}{T_{sk} + 273} + 8.997 \qquad (A7)$$

Equation A7 was modified from Ref. 49, p. D-171 and D-176; constants were modified to give very accurate results between 20 and 45°C (A = 10391.513; B = 8.9969562); numerator was obtained by multiplying $A \cdot (-0.2185)$.

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