Size DOES Matter:

A Calculus of Differences Between Children and Adults

Robert S. Holzman MD, FAAP
Senior Associate in Anesthesia, Children's Hospital
Associate Professor of Anaesthesia, Harvard Medical School
Boston, MA 02115

Pediatric anesthesia is a demanding branch of anesthesiology. While a comparison between children and adults is of interest for the "adult" anesthesiologist, particularly if he or she only occasionally anesthetizes children, it is the "raison d'être" for the pediatric anesthesiologist.

Let's think about the fundamental differences between children and adults in terms of the currency of life – oxygen - and how perturbations of the oxygen economy help us understand the temporary state we call "anesthesia." While this very focused approach may not be completely reliable for the myriad of human diseases, it might be just the compass we need for the practice of anesthesiology and critical care, because it should shed some light on the mathematical differences between children and adults (i.e., why children are not simply "little adults") and how these concepts can be put to practical use in the operating room.

In 1638, Galileo proposed his Principle of Similitude:

> "The creatures of Earth must be approximately sized and shaped to the planet through the effects of gravity and chemistry, which vary as the creatures are large or small, fat or thin."

First of all, what does size mean? Is it mass, weight, surface area? Pediatric anesthesiologists especially are used to body weight as the standard for pharmacological and physiological calculations. It has been recognized for a long time that pharmacological and biological values are larger on a per-kg. basis for infants and children than adults.

What does life mean? I don't know (maybe it is just a bowl of broccoli – you will see what I mean later). If we go back to the oxygen economy, then life is a thermodynamically unstable system that cannot be maintained unless energy is continuously added. Moreover, living matter is constantly engaged in performing various kinds of work – movement, chemical synthesis, transport of substances against concentration gradients, etc. Homeotherms need energy to maintain body temperature, and obtain it from the energy-supplying reactions of carbohydrate, fat and protein digestion.

Early on, it was clear that metabolism was not linearly related to body weight. Basal heat production per unit body weight in homeotherms decreases rapidly with increasing weight. Thus, the basal metabolism per unit weight of small animals such as mice and canaries is 20 to 25 times as great as of large animals, such as cattle. According to the laws of Newton and Stefan-Boltzmann, the rate of cooling of a body is proportional to its surface area. If the heat loss is proportional to

the surfaces, then the heat production must likewise be proportional to the surfaces, since in homeotherms heat production must equal heat loss. Homeotherms must therefore have developed a heat production control to function in proportion to surface area. This is, at least, the evolutionary logic of the surface law. Rameaux and Sarrus first formulated this relation of heat production to linear size and to surface area more than 150 years ago. Their presentation to the French Royal Academy of Sciences suggested:

1. An equality between heat loss and heat production in homeotherms.
2. Heat loss proportional to free surface.
3. Heat production proportional to oxygen consumption.

Since heat loss and heat production are proportional to free surface and since surfaces vary with the squares of the homologous sides, oxygen consumption, heat production and heat loss should be proportional to the corresponding dimensions of the animals.

Expressed mathematically, if we let y = Surface, *or* heat loss, *or* heat production, *or* oxygen consumption and let L = linear size, then

$$y \alpha L^2$$

Or in more general terms, if an equality is created instead of a proportion:

$$y = aX^b$$

If S, surface area, varies with the square of the linear size, L, then:

$$S \alpha L^2$$

and volume or weight, W, varies with the cube of linear size, then:

$$W \alpha L^3$$

Transformed, linear size is the cube root of weight:

$$L \alpha W^{1/3}$$

and surface area, S, is therefore proportional to the 2/3 power of weight:

$$S \alpha L^2 \alpha (W^{1/3})^2 \alpha W^{2/3}$$

Converting the proportionality to an equality, we get:

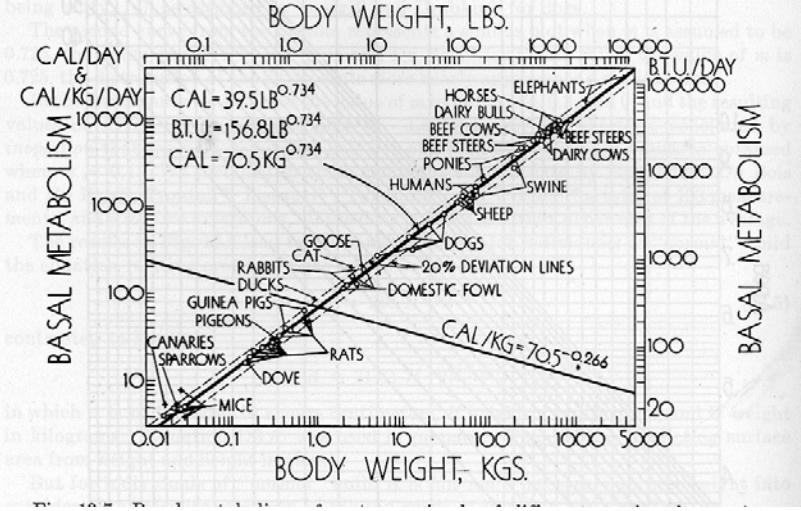
$$S = aW^{2/3}$$

Therefore, ***the influence of body size on metabolism may reasonably be related to oxygen transport.*** And oxygen transport, through a variety of branching tubular networks such as the respiratory and cardiovascular systems, resembles – a fractal network. (unfortunately unknown to Sarrus and Rameaux at the time.) But I am getting a little ahead of myself here.

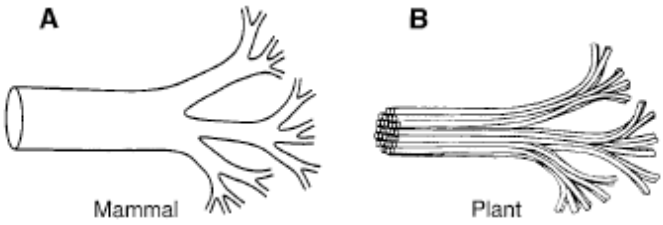
There are a few caveats. The surface area of a living animal is not constant. Surface area as it relates to heat loss changes with environmental temperature – in animals because of rolling up or spreading out, and also because heat-conserving and heat-dissipating mechanisms are initiated. This is minimized during anesthesia. While it is true that surface area varies with the 2/3 power

of weight, this is only for geometrically similar bodies of constant specific gravity; and small and large, young and old, fat and thin animals – especially of different species – may vary geometrically and also may not be of constant specific gravity. You can't simply assume that adults and children are geometrically similar, because they are not; infants have short stumpy legs, relatively big heads and large body trunks and the surface area formula underestimates the measured surface area in children with a predicted surface are of less than 1.3 m^2. However – and here is an interesting paradox – the body area of animals rises more slowly than the surface law would suggest, because larger animals are stockier. (Galileo, again, and the influence of gravity). Also, relating metabolism to body size prompts a subtle cause and effect relationship that simply does not exist – after all, it is not the body surface area that causes the differences in basal metabolism but rather a variety of neuro-endocrine responses.

Therefore, it is still an oversimplification to accept body surface area as a reference base, and the very specific concept 2/3 power of weight does not hold as well as the more general principle W^b as in the original proportional equation, a value yet to be determined based on empirical data. For that, we have to go back to a time when this was first obtained in animal husbandry by Brody, who actually measured the relationship between body mass and basal metabolism and found that the 3/4 power of weight predicted metabolic demand much better. It even plotted out a straight line on log-log paper! His contemporary, Kleiber, also suggested that the 3/4 power of body weight should be utilized in an exponential expression such as $y = aX^b$



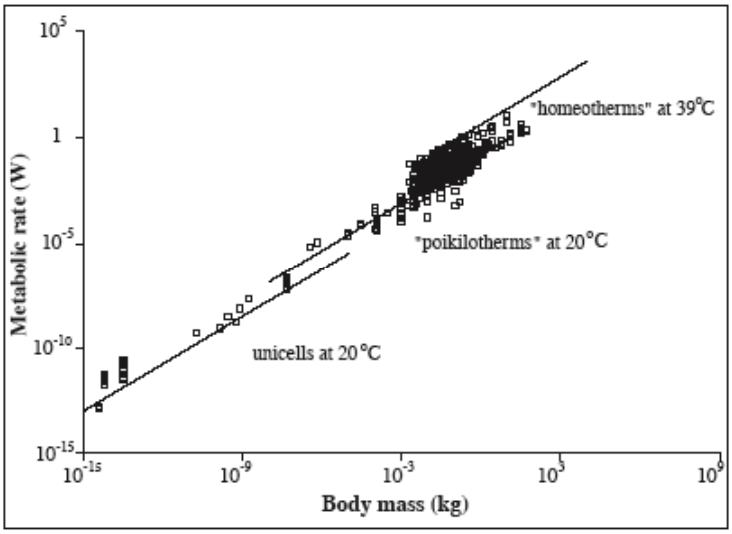
So, the surface area model ultimately doesn't fit empirical investigations by Brody. Why? The body area of animals rises more slowly than the surface law would suggest, because larger animals are stockier. The "surface" law, after all, refers to an animal's skin. Surfaces used in energy exchange such as gut villi or respiratory alveoli (in animals) or even transport systems in plants bear more of a relationship to branching tubes – a fractal! This goes along with empirical evidence developed by Brody and Kleiber in the 1930's and 1940' suggesting that the appropriate scaling factor is closer to .75 rather than .67.



a natural, 3 dimensional fractal

Lindahl et al found that in anesthetized spontaneously breathing children, VCO_2 and VO_2 were 11.4±3.1 ml-kg$^{3/4}$ and 14.2±3.9 ml-kg$^{3/4}$ respectively. Therefore, VO_2 for infants and children up to a body weight of 20 kg could be based upon 14 X kg$^{3/4}$ during halothane anesthesia and surgery. Interestingly, the minimum flow rate of 250 ml/minute established for anesthesia machines when calculated for a 70 kg. adult, is equal to 10.5 X kg$^{3/4}$.

Recently, this branch of mathematics, allometry, has been "re-discovered" by biophysicists and validated empirically for homeotherms, poikilotherms, unicellular forms and even plants – a consistent approach for the biosphere!

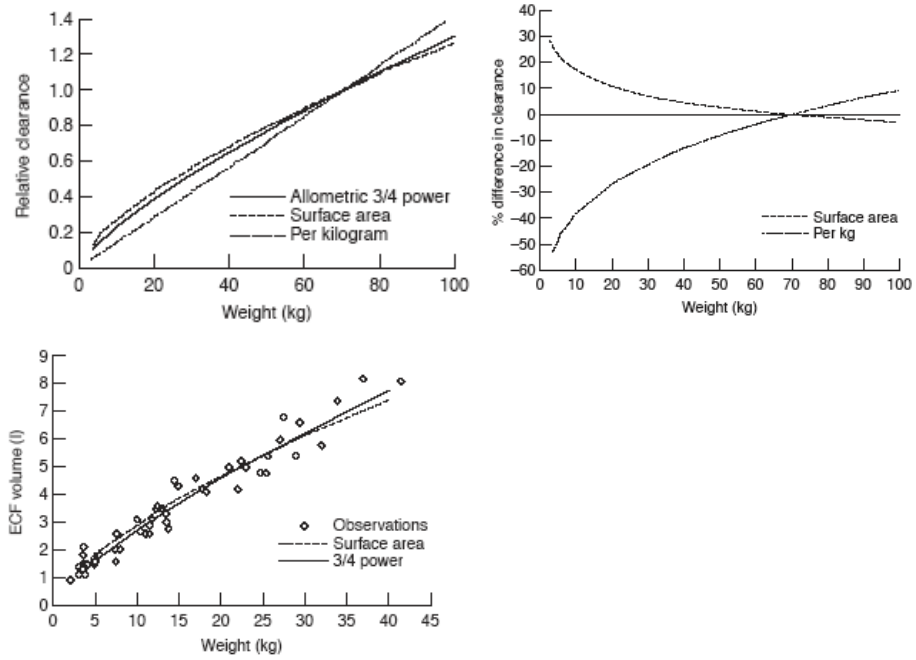


(from Science 2001;293:1)

Relating allometric scaling to pharmacology

Extracellular fluid volume, previously thought to be related to body surface area, actually scales to the .75 power better. We can accept this notion on a general basis because the volume of a cylinder is $V = h\pi r^2$ which is of the general form $y = aX^b$.

The original paper by Friis-Hansen describing the relationship between extracellular fluid volume in infants and children and relating it to BSA had the right concept but the data were never subjected to nonlinear regression analysis. Doing so, one finds that the "goodness of fit" of the original data is improved if the exponent used is .75 rather than .67. For pharmacokinetic calculations dependent on the ECF, such as clearance, dosing (e.g., to ED_{90}) and volume of distribution (V_{dss}), the allometric scaling model fits better than either the BSA or "per-kg." linear model.

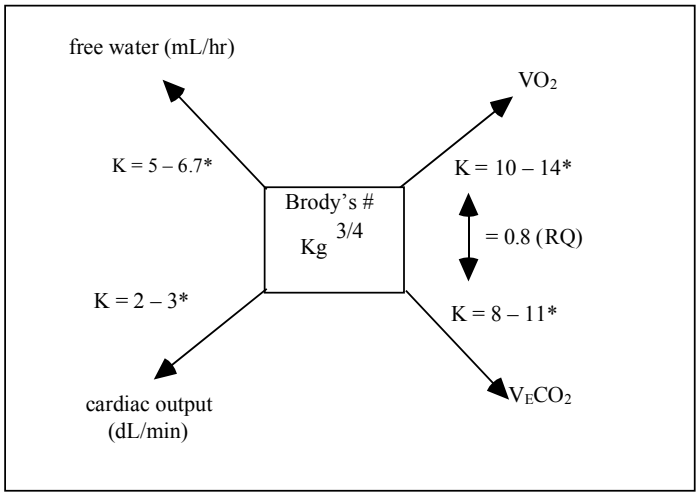


(all from Anderson BJ, Meakin GH: Paed Anaes 2002;12:205-19)

On the other hand, there are pharmacodynamic as well as pharmacokinetic issues. Clearance, for example, is reduced in neonates and infants, even when standardized to an allometric or surface area model. Increased sensitivity (pharmacodynamic factor) is one cause, possibly related to a decrease in quantal release of acetylcholine.

Relating allometric scaling to Physiology

The estimate for oxygen requirement in a basal state is based on Brody's number, the $kg^{3/4}$. Metabolic oxygen consumption (VO_2), CO_2 production (V_ECO_2), free water requirement and the cardiac output (dL/min.) can be calculated from Brody's number. Body temperature, among other factors, will influence this calculation, with the direction of oxygen consumption changing approximately 7% for each degree ^oC increase or decrease.



* Age-dependent; in general, the constant k is greater the younger the patient

For example, if Brody's number and it's clinically useful derivatives was calculated for a 70 kg. adult:

Body weight (kg)		70.0
Brody's #	$kg^{3/4}$	24.2
Oxygen consumption (mL/min)	Brody's # X 10	242.0
Minute CO_2 production (mL/min)	Brody's # X 8	193.6
Free water requirement (mL/hr)	Brody's # X 5	121.0
Cardiac output (dL/min)	Brody's # X 2	48.4

The rate of CO_2 production will be related to the rate of oxygen consumption by the RQ (in most circumstances) and can aid in the precise calculation of minute ventilation requirements. For the above example:

Calculate the minute volume required for normocarbia in the 70 kg. adult above:

Brody's #	$kg^{3/4}$	24.2
Minute CO_2 production (mL/min)	Brody's # X 8	193.6
Normocarbia (% atm)	5 %	
V_A for normocarbia (mL/min)	$V_eCO_2/.05$	3872
$MV = V_A + V_D$ (mL/min)	$\approx 3\ V_A / 2$	5808

Because V_ECO_2 and minute ventilation are related to VO_2 by the respiratory quotient, ventilatory requirements significantly out of proportion to "normal" or expected amounts may accompany a hypo- or hypermetabolic state such as hypothyroidism or malignant hyperthermia, respectively.

In homeotherms, water is required for the elimination of heat generated during metabolic activity, and water loss is normally 100 mL for every 100 kcal expended. Approximately 70 mL is lost as urine, with 30 mL lost through the skin, 15 mL through respiration, and 15 mL *produced* through metabolism. Therefore, free water requirements are ultimately proportional to caloric demands, which are decreased when patients are anesthetized. Water requirements can therefore be calculated in relation to basal metabolic demand according to the following:

(1) The consumption of 1,000 ml of oxygen generates 4,825 calories.
(2) If VO_2 is equal to $10 \times kg^{3/4}$ (mL /min) in adults, then heat production per hour is:
(3) $\frac{10 \times kg^{3/4}}{1{,}000} \times 4{,}825 \times 60$
(4) the calories required for 1 mL of water to evaporate are 63 cal. This plus 540 calories are required to achieve the heat of vaporization (total 603 cal / mL of water). This modifies the above equation to: mL water / hour $= \frac{10 \times kg^{3/4} \times 4{,}825 \times 60}{1{,}000 \times 603}$

$\approx 5 \times kg^{3/4}$

which parallels basal oxygen consumption, once again.[15]

When calculating metabolic requirements in children, the constant k can be adjusted in the following fashion:

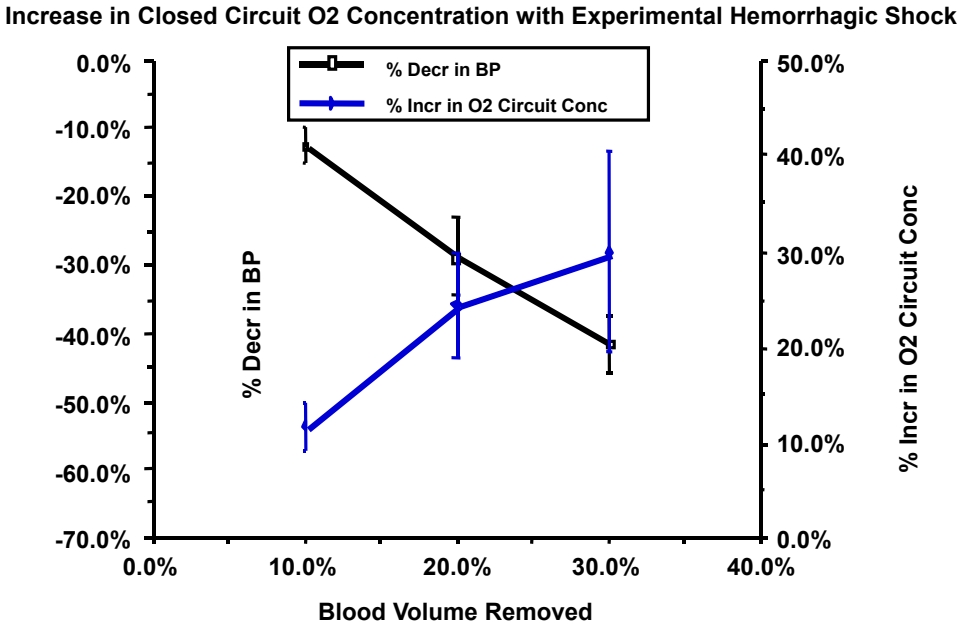
In a 22 kg. five year old patient:

Body weight (kg)		22.0
Brody's #	$kg^{3/4}$	10.2
Oxygen consumption (mL/min)	**Brody's # X 14**	142.8
Minute CO_2 production (mL/min)	**Brody's # X 11**	112.2
Free water requirement (mL/hr)	**Brody's # X 6.7**	68.0
Cardiac output (dL/min)	**Brody's # X 3**	30.6

Closed Circuit Anesthesia as a Homeostasis Monitor

Closed circuit practice emphasizes *the maintenance of a constant anesthetic state by the addition of gases and vapors to the breathing circuit at the same rate that the patient's body redistributes, stores and eliminates them.* The closed circuit anesthetic approach emphasizes the *amount of vapor or gas needed* to maintain a constant alveolar and arterial concentration. Again, in thinking about the balance of oxygen supply and utilization, with the volume of the system constant and the oxygen concentration maintained in a steady state at the appropriately selected value, *the oxygen analyzer becomes a monitor of metabolic oxygen consumption.* An increase in mean circuit oxygen concentration reflects an excess of O_2 delivery compared to metabolic demand.

Likewise, a decrease in mean circuit oxygen concentration reflects an increase in the patient's oxygen demand.



The amount of oxygen to be delivered by the anesthesia machine in order to achieve this steady state can be calculated using the above strategy, based on allometric scaling.

With the ventilator bellows filling just prior to the next ventilatory cycle, the bellows themselves become a sensitive monitor of diaphragm activity, as respiratory efforts can easily be detected by watching bellows movement. Moreover, the expiratory flow rate is more accurately reflected in the bellows of a low-flow system because the patient's exhalation volume provides the bulk of the gas in the bellows – the rate of ascent of the bellows directly reflects the rate at which the patient exhales. Bronchospasm or airway obstruction is more easily detected and noting the change in the fill rate of the bellows more easily monitors therapeutic interventions. Finally, movement of the bellows is a sensitive monitor of the degree of neuromuscular blockade, because the diaphragm recovers from neuromuscular blockade before the peripheral muscles.

Cost Containment

Assuming that fresh gas flow is reduced to closed circuit levels based on allometric calculations, a significant reduction in the expenditure for the costs of potent inhaled agents can be realized. The costs of inhalation anesthesia are primarily related to the agent selected, the concentration delivered, the duration of the anesthetic and the total FGF rate. At a 3 liter FGF, a 1 MAC-hour anesthetic of halothane would cost about $ 0.40, isoflurane more than $ 9.00, and desflurane more than $ 16.00. The same anesthetic at a 1 liter FGF would cost $ 0.14, $ 3.13 and $ 5.38 respectively.

Philosophical Statement (*in lieu of* a Conclusion)

Humans caring for other humans have developed systems of understanding and calculation primarily based on linear mathematics. This may be because arithmetic (isometry) and Euclidian geometry preceded Galileo and scaling (allometry), and it may even have something to do subtly with the linear calculations such as the Van't Hoff equation used in biological thermodynamics. The mathematics of biological modeling is still infantile compared with mathematical modeling in the inaminate sciences, such as inorganic chemistry.

Our daily drug calculations – dosing, clearance, volume of distribution; our physiological calculations – oxygen consumption, CO_2 production, water requirements, cardiac output – are all based on linear math, despite a great deal of evidence (and none of it particularly new evidence) to the contrary. Will it ever change? Probably not.These nonlinear functions are difficult to calculate mentally at the workplace; calculators, or at least nomograms, are required, as well as a significant shift in framework.

But what a great, unifying explanation for "why."

Table 1. Values of allometric exponents for variables of the mammalian cardiovascular and respiratory systems predicted by the model compared with empirical observations. Observed values of exponents are taken from (*2*, *3*); ND denotes that no data are available.

Cardiovascular			Respiratory		
Variable	Exponent		Variable	Exponent	
	Predicted	Observed		Predicted	Observed
Aorta radius r_0	3/8 = 0.375	0.36	Tracheal radius	3/8 = 0.375	0.39
Aorta pressure Δp_0	0 = 0.00	0.032	Interpleural pressure	0 = 0.00	0.004
Aorta blood velocity u_0	0 = 0.00	0.07	Air velocity in trachea	0 = 0.00	0.02
Blood volume V_b	1 = 1.00	1.00	Lung volume	1 = 1.00	1.05
Circulation time	1/4 = 0.25	0.25	Volume flow to lung	3/4 = 0.75	0.80
Circulation distance l	1/4 = 0.25	ND	Volume of alveolus V_A	1/4 = 0.25	ND
Cardiac stroke volume	1 = 1.00	1.03	Tidal volume	1 = 1.00	1.041
Cardiac frequency ω	−1/4 = −0.25	−0.25	Respiratory frequency	−1/4 = −0.25	−0.26
Cardiac output $\dot{E}$	3/4 = 0.75	0.74	Power dissipated	3/4 = 0.75	0.78
Number of capillaries N_c	3/4 = 0.75	ND	Number of alveoli N_A	3/4 = 0.75	ND
Service volume radius	1/12 = 0.083	ND	Radius of alveolus r_A	1/12 = 0.083	0.13
Womersley number α	1/4 = 0.25	0.25	Area of alveolus A_A	1/6 = 0.083	ND
Density of capillaries	−1/12 = −0.083	−0.095	Area of lung A_L	11/12 = 0.92	0.95
O_2 affinity of blood P_{50}	−1/12 = −0.083	−0.089	O_2 diffusing capacity	1 = 1.00	0.99
Total resistance Z	−3/4 = −0.75	−0.76	Total resistance	−3/4 = −0.75	−0.70
Metabolic rate B	3/4 = 0.75	0.75	O_2 consumption rate	3/4 = 0.75	0.76

from West GB, Brown JH, Enquist BJ. Science 1997;276:122-6

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