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Technical Note

Metabolic Scaling Law for Fetus and Placenta

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ABSTRACT

The human fetal birth weight does not scale linearly with the weight of the placenta, but exhibits an allometric scaling consistent with Kleiber's Law for the basal metabolic rate. We discuss the possible causes of such scaling, and its clinical consequences. In particular, we show that the value of the scaling exponent is an indicator of a normal fetoplacental development.

1. Introduction

1.1. Kleiber's Law for scaling of the basal metabolic rate

Kleiber's Law is named after the ground-breaking work of Max Kleiber [1,2] in the early 1930s, who postulated that the basal metabolic rate B of an organism is proportional to its mass M raised to the power $^3/_4$:

$$B \sim M^{3/4}.$$

This law, discussed in detail in Kleiber's book *"The Fire of Life"* (1961) [3] has attracted both attention and controversy. The prevalent theory at that time (which has not yet been put completely to rest) was known as the *surface theory* of metabolism. It appeals to seemingly simple geometric considerations that suggest the scaling exponent 2/3 (rather than $^3/_4$). For example, let us make the simplifying assumptions that the body of an organism is a three-dimensional ball, and all of its metabolic exchange occurs via heat transfer through its spherical surface. Then the mass is proportional to the third power of the diameter of the ball, and the surface area is proportional to the square of the diameter. Thus the scaling equation under these assumptions would be

$$B \sim M^{2/3}.$$

A similar argument has to do with the internal surfaces of the organism, where the oxygen and nutrient exchange takes place – they are again assumed to be proportional to the whole body surface.

However, Kleiber found that $^3/_4$ was generally in a much better agreement with experiment, as we confirm below. There are many errors in the arguments in favor of surface theory. A detailed refutation is found in Kleiber's book [3].

1.2. Fractal structure of the vasculature and metabolic scaling

In 1997, G.B. West et al. [4] proposed an explanation of Kleiber's scaling exponent based on the fractal nature of the vasculature. After making several simplifying assumptions, they derived $^3/_4$ from considerations of hydrodynamic optimality of the vascular network. This work has attracted a lot of criticism (see [5] as an example). However, the work of West et al. appears to us as a step in the right direction, even if the model details are arguable. The explanation of a non-trivial scaling law based on spontaneously emerging fractal structure of an organism is consistent with well-understood examples in physics (see an excellent review [6] for other physical and biological examples).

It is important to note that at least some of the controversies around $^3/_4$ scaling can be attributed to the difficulty in *defining and measuring* the basal metabolic rate of an organism. Metabolism was also historically thought of as heat exchange (as noted from the units in which metabolic rate is measured – *calories/s*). On the other hand, the analysis of West et al., for example, is entirely based on blood flow considerations.

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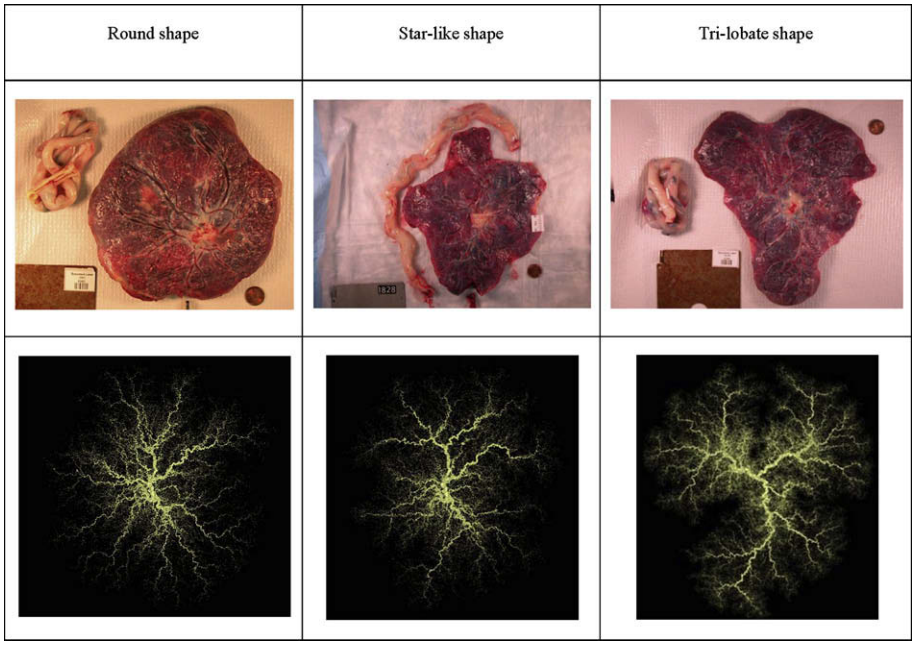

Fig. 1. Common placental shapes studied in Ref. [12]. Top row – placentas, bottom row – models of their vascular trees.

2. Methods

2.1. Metabolic scaling for human placenta

In 1966 Ahern, as cited in Ref. [7], proposed a variant of metabolic scaling law for human pregnancy. He proposed replacing the basal metabolic rate of a fetus with the placental mass *PM*, which should result in a scaling relation of the following kind (here *FM* stands for the body mass of the fetus):

$PM \sim FM^{\beta}$.

This step is very significant, for two reasons. First, it removes the main obstacle in exactly defining what constitutes metabolic exchange, and measuring basal metabolic rate: *whatever energy is exchanged by the fetus must pass through the placenta.* Secondly, it leads to a measurement of the basal metabolic rate which does not require sophisticated laboratory apparatus to gauge the caloric intake and expenditure of an organism. Note that the measurements used in Kleiber's original work used tens (if not less) organisms of each kind. Ahern conjectured $\beta = 2/3$ for reasons already familiar to us.

Of course, *FM* is routinely recorded at birth. *PM* is also frequently recorded at birth, and is often combined with *FM* to yield the measurement known as *fetoplacental ratio (FPR)*. This is defined either as ratio of the mass of the placenta to that of the baby, or its inverse. It is commonly used for analysis of fetal pathologies, see for instance, the study in Ref. [8]. To fix the ideas, we will set

$FPR = FM/PM$ measured at birth.

3. Results and discussion

3.1. Fetoplacental version of Kleiber's Law

Recently, in Ref. [9], we have studied the scaling relation between *PM* and *FM* using the data collected by the National Collaborative Perinatal Project. In all, over 26 thousand pairs (*FM*, *PM*) were recorded. The results are in a remarkable agreement with Kleiber's Law:

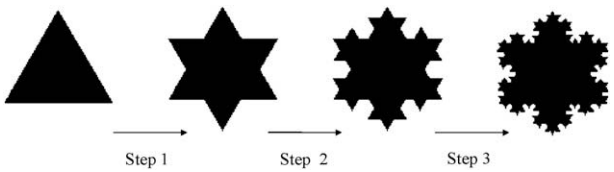

Fig. 2. A few steps in the construction of Koch Snowflake.

$$PM = \alpha FM^{\beta}, \text{ with } \beta = 0.78 \pm 0.02, \ \alpha = 1.03 \pm 0.17$$

We should make a note, which Kleiber makes explicit in his book [3] on page 214, that until there is an accepted explanation of the specific value of the scaling exponent (such as that proposed in Ref. [4]), we cannot assume that the value $^3/_4$ is exactly correct. While it is a "nice number", so is $\pi/4$ – and we would not be able to discern a measurable difference between the two from the data. However, the value $^3/_4$ is preferable from practical considerations, as it is easier to calculate. Having said this, we turn to the practical aspects of applying the scaling law.

3.2. Consequences for measuring FPR

The scaling relation

$PM \approx FM^{0.75}$

implies that *FM* grows *faster* than *PM* in a normal fetal development. For instance, a normally developed fetus will have a larger *FPR* later in gestation. Since a low *FPR* is usually taken as a sign of poorer fetal growth and likely placental pathology, the findings based on *FPR* will be biased to favor newborns with a larger *FM*. For instance, a normally developed baby with a birth weight of *3000* g will have mean *FPR* of almost *7.5% lower* than a baby with a birth weight of *4000* g. The difference for babies born weighing *2000* and *4000* g is almost *20%*. To correct for this, the *FPR* should be replaced with a ratio reflecting the true scaling exponent:

$$FPR_{\text{corrected}} = FM^{0.75}/PM.$$

It is a coincidence that the mean value of α obtained in our study is so close to *1*. There is no deep meaning to this, only a fortuitous choice of units for measuring masses (if we had elected to measure masses in ounces, for instance, the coefficient α would have the value of approximately *2.37*). In practice, however, it is useful, as it gives a simple prediction: *the normal value of* $FPR_{\text{corrected}}$ *is 1*. It also gives a simple recipe for measuring the scaling exponent β:

$\beta \approx \log PM / \log FM$

3.3. Correct scaling as an indicator of normal development

It is reasonable to assume, that a deviation from the $^3/_4$ scaling law would be associated with a variation in the normal fetal–placental development. A simple indicator of a normally developed placenta is its shape. A typical placenta is round, with a centrally inserted umbilical cord [10,11]. In Ref. [12], we have studied correlation between a violation of $^3/_4$ law, and non-roundness of the placenta. Two measures of placental shapes were used. The standard deviation of the radius of the placenta, calculated from the insertion point of the umbilical cord is the most obvious measure of roundness. The other one, which we call *roughness*, is calculated as the perimeter of the placental surface, divided by the perimeter of the smallest convex hull that contained the surface. It is equal to 1 for any convex shape, such as a circle, and thus measures deviation from convexity of the placental shape. We have found in Ref. [12] that both of these measurements are strongly and significantly correlated with $\Delta\beta$, which is the difference from the measured value of β and $^3/_4$.

In Ref. [12] we have speculated that a deformed placental shape may be caused by a variation in the development of the placental vascular tree. We developed a dynamical growth model of a placental vasculature, and demonstrated that a change in the *branching density* of the tree results in one of several common deformed shapes (see Fig. 1).

3.4. Predictive powers of the value of the scaling exponent

To test the predictive power of the scaling exponent β, we have carried out tests of statistical correlations of β in the dataset of [12] with maternal pre-existing diabetes, pre-eclampsia, and chronic hypertension, each a disorder recognized to affect the maternal vasculature either before or early during pregnancy [13–15]. All were strongly correlated with the value of β. For pre-existing diabetes the correlation was 6%, for pre-eclampsia it was 11%, for hypertension it was 12.5%. These correlations were very statistically significant. Thus, each of these conditions leads to a higher value of the scaling exponent β, which means that the weight of the newborn is *less* than predicted by Kleiber's Law, so the placenta has a *decreased metabolic efficiency*.

As another piece of evidence here, we considered the standard radial deviation from the *geometric center* of the placental surface. It is not significantly correlated with $\Delta\beta$. The geometric center has no particular significance in the internal structure of the placenta, whereas the insertion point of the umbilical cord is the root of the vascular tree. Thus we see that variation in the scaling is related to the deformations in the shape of the vascular tree, and not a deformed surface shape *per se*.

3.5. How the vascular branching affects the scaling

The branching fractal structure of the placental vasculature leads to a scaling exponent which is higher than the value $2/3$ predicted by the surface theory. To illustrate how the fractal structure of the circulatory network can impact the metabolic rate, let us look at a toy model of a two-dimensional organism, whose mass is proportional to the surface area, and whose basal metabolic rate measures energy exchange through its one-dimensional boundary (the "surface"), and is thus proportional to the perimeter.

As a first example, consider an organism shaped as a disk. Given that the area scales as the diameter squared, and the perimeter scales as the diameter to the first power, we will have $B \sim M^{1/2}$ in this case.

As a second example, consider an organism shaped as a simple fractal, known as *von Koch snowflake*. To construct this shape, one takes an equilateral triangle with side a, and attaches an equilateral triangle of side $a/3$ in the middle of each of the three sides (Fig. 2, Step 1). The procedure is then repeated by attaching a triangle of side $a/9$ in the middle of every boundary segment, and so on (Fig. 2, Steps 2 and 3). We stop adding new decorations to the snowflake at the step n, when the size of the new decoration $a/3^n$ becomes smaller than some cutoff value l_0 (the smallest biological scale of our organism).

It is easy to see that the area of our snowflake still scales as the square of the diameter. But the perimeter will no longer be proportional to the diameter. Instead, we will have

$$\text{perimeter} = \text{diameter}^{\gamma}, \text{ where } \gamma = \log 4/\log 3 > 1.$$

The longer perimeter means a larger metabolic scaling rate for our toy organism: $\beta \approx 0.63 > 1/2$. Thus, the fractality of the circulatory network increases the rate of the metabolic exchange.

In our model of placental vascular growth [12], the deformed placental shapes (Fig. 1) were obtained by suppressing the branching of the vascular tree at various moments in gestation. This leads to a less efficient fetoplacental metabolism, which results in a larger value of β, as we have observed above.

3.6. Concluding remarks

In Ref. [9] we established a fetal–placental version of Kleiber's Law, and in Ref. [12] we demonstrated its connection with the structure of the placental vasculature. This has several important practical consequences. The value of the scaling exponent β is easy to calculate. It is also, as we have seen, a significant indicator of a normal fetal–placental growth. Variation in β correlates strongly with an abnormality of the branching structure of the placental vasculature (manifested by an abnormal placental shape [12]). It also correlates strongly with maternal diseases such as diabetes, pre-eclampsia and hypertension, which are known to affect placental vascular growth. We have further shown how the scaling introduces a bias into the value of the FPR, and proposed a correction to account for this. From a purely theoretical point of view, our study seems to conclusively confirm Kleiber's Law in fetal–placental setting. As to the origins of the scaling law, our findings offer a strong support to the relation between $^3/_4$ scaling and the structure of the vasculature, similar to what has been proposed in Ref. [4], and hinted at in the original work of Kleiber [3].

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