Comparative hemorheology

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Abstract. Comparative data on blood composition and blood flow properties indicate different levels of interspecies variation for several parameters. Hematocrit and hemoglobin levels have relatively low variability among mammals, while mean cell volume and red blood cell (RBC) count are more variable. There is also a difference of variability between high and low shear rate blood viscosity in mammals, with low shear rate viscosity having a higher degree of interspecies variation. This observation parallels the diversity of RBC aggregation among mammalian species. Allometric relations for blood rheology parameters indicate highly significant correlations of low shear rate blood viscosity and RBC aggregation with body weight, especially if species belonging to the order Artiodactyla are excluded. These allometric relations can be used to formulate various hypotheses about the evolutionary histories of circulatory functions, as well as hypotheses related to the role of RBC aggregation in the mammalian circulatory system. Such comparative studies and analytical reasoning based on comparative data may contribute to answering the “why” questions, and accordingly may improve our understanding of circulatory functions and hence may have possible clinical importance. During the last several decades, similar approaches to various medical concepts have yielded a new approach to medicine that is now known as Evolutionary Medicine.

Keywords: Evolution, darwinian medicine, comparative physiology, blood rheology, hemodynamics

1. Introduction

“Orgel’s second rule: Evolution is cleverer than you are.”

Francis Crick quoted by Daniel C. Dennett (1984)

Comparative studies of physiological functions and mechanisms are widely applied approaches to describe the diverse ways of meeting functional requirements by different species and the many different adaptations to challenges encountered during evolutionary history. Such an approach may lead to broad biological generalizations that can be applied to groups of species (e.g., primates, mammals) and also may help in identifying animal preparations that are particularly suitable for studying a specific function. The above comment regarding comparative physiology adapted from Prosser [28] sets the basis for any type of comparative studies including the field of hemorheology. This approach provides the opportunity for using different species as study variables and allows investigators to make use of nature’s experiments. Therefore, comparative studies are not only driven by pure curiosity, but are usually aimed at understanding the logic behind interspecies variations for a given parameter or trait and the relations between various parameters and traits, thereby aiding our understanding of basic physiological principles [14].

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Fig. 1. Mean cell volume (MCV) plotted against red blood cell count (RBC) for a wide range of species including mammals and birds. Note the inverse association suggesting that their product $[(RBC) \times (MCV)]$, which reflects hematocrit, remains constant. Reproduced from Gaskoyne and Hawkey [15] with permission.

2. Variation in blood parameters among species

Interspecies variations of blood parameters have been explored utilizing databases for a wide variety of species [15, 27]. Such comparisons usually limit the analysis to within a given class (e.g., Mammalia) since there are very diverse properties of blood cells among different non-mammalian classes (e.g., nucleated red blood cells). RBC-related parameters can be classified into two groups based on their coefficients of variation (CV). One group is composed of parameters with relatively small CV: hematocrit, hemoglobin and mean corpuscular hemoglobin concentration (MCHC) are characterized by interspecies CV of 14.8, 17.4 and 9.3%, respectively. The other group includes RBC count, mean cell volume (MCV) and mean corpuscular hemoglobin (MCH) with CV values ranging from 37–40% [27]. Gaycoyne and Hawkey reported very similar CV values for a slightly larger group of species [15].

Such a pattern of interspecies variations for RBC parameters underlines the concept of an optimal range of hematocrit [13], which seems to be valid for the entire range of mammalian species. This concept is based on the opposing effects of hematocrit on oxygen carrying capacity and blood viscosity: increased hematocrit raises oxygen carrying capacity but also raises blood viscosity and hence resistance to flow. RBC parameters affecting hematocrit, especially MCV and RBC count, appear to have evolved in a reciprocal relationship (Fig. 1) in order to maintain hematocrit and hemoglobin values within an optimum range. The evolution of MCV in various species appears to reflect different adaptations to environmental challenges [27].

Johnn et al. reported blood viscosity measured at high and low shear rates for a wide range of mammals [20] and indicated a very significant difference in the distribution range of the values: high shear rate (128.5 s^{-1}) viscosity had a lower CV (19.0%) compared with low shear rate (0.277 s^{-1}) viscosity (75.4%) [20]. It should be noted that high shear rate blood viscosity is mainly affected by RBC deformability, whereas low shear viscosity reflects the influence of RBC aggregation [11]. Baskurt et al. reported a meta-analysis of estimated RBC aggregation parameters for 22 mammalian species, with the estimates based on several comparative studies [10]. The interspecies CV of these aggregation parameters was 82.7% and thus slightly higher than the CV for low shear viscosities reported by Johnn et al., possibly reflecting variability introduced due to using different instruments for the determination of RBC aggregation.

Only limited comparative data for RBC deformability in different species exist in the literature. Smith et al. reported that the elongation index for 18 species exhibits a large variation, especially horse and goat RBC having deformability curves significantly different from the others [31]. Windberger and Baskurt report that the shear stress required for one-half maximum RBC deformation, an index reflecting cell deformability [4], had a CV of 75.4% for nine species and thus much greater than for high shear viscosity [37]. However, it should be noted that these comparative evaluations involved different numbers of species; the data for RBC deformability are limited to a small group and thus do not include the wide range used by Johnn et al. [20]. Therefore, while these comparative findings may be internally consistent, they may not be appropriate for other groups; such limitations due to lack of available data are frequent problems in comparative studies [27].

Interspecies correlations between hemorheological parameters and characteristics of red blood cells (e.g., MCV, MCH, MCHC), as well between other cellular properties which may affect certain RBC flow properties (e.g., surface charge density), have been recently discussed elsewhere [9] and are not presented in detail here. In brief, it has been argued that the patterns of interspecies differences in hemorheological behavior cannot be explained merely by the variation of cellular properties. Further evaluation of interspecies patterns for parameters reflecting the structural and flow properties of blood may reveal valuable information about the evolution of circulatory functions.

3. Allometric approach for the evaluation of interspecies differences in hemorheology

Interspecies investigations of morphological and physiological parameters reveal a wide range of differences. Many of these parameters or species-specific traits (e.g., maximum life span) can be described as a power function of body mass [19, 26, 34], an approach known as allometry [18]. The allometric approach provides the basis for a generally-effective rule for a given parameter or trait, and it is especially interesting to identify outliers since they have the potential for indicating various different evolutionary adaptations to diverse environmental conditions [27]. Furthermore, investigating the co-variation between parameters and/or traits after mathematically removing the effect of body mass may provide insight into specific developments in response to different evolutionary drives [27].

The allometric approach has been applied to a wide variety of parameters including metabolic rate [22], circulatory factors such as the dimensions of the circulatory system and the heart, and several functional parameters [19]. For many parameters, the allometric relationships can be represented using logarithmic scales and by a power function in the form of $y = a \cdot W^b$ where W is the body weight of the species and a and b are regression coefficients [19]. Morphological parameters can be characterized by allometric equations with the exponential coefficient (b) being around 0.75, and many physiological functional

Fig. 2. Whole blood viscosity measured at 128.5 s^{-1} for 27 mammalian species versus log body weight. Viscosity data were derived from Johnn et al. [20] and body weight data from <http://genomics.senescence.info>. Pearson r is 0.129 ($p > 0.05$), indicating a non-significant association between high shear viscosity and log body weight.

parameters, including those related to circulatory function (e.g., heart rate), fit allometric relations with an exponent of about 0.25 [19].

Blood parameters have been the subject of comparative investigations using the allometric approach as early as 1875 [17]. Gulliver reported correlations between RBC and body size among mammalian species within orders [17], although this relationship was not confirmed by others [12, 29]. However, Promislov et al. did report significant relationships between blood parameters and body mass within different taxons using an independent-comparisons method to identify interspecies differences [27]. This method is based on comparisons of species at each bifurcation of a phylogenetic tree, assuming that the two species at a given node share a common ancestor and the difference between them reflects an evolutionary change [27].

The application of an allometric approach to blood rheology parameters has been very limited. Li reported that blood viscosity is independent of body weight but did not indicate the shear rate used for the measurements [19]. We have used the low and high shear rate viscosity data presented by Johnn et al. [20] to investigate allometric relationships. These results are presented in Fig. 2 for blood viscosity measured at a high shear rate (128.5 s^{-1}) versus log of body weight for 27 species: no significant correlation was detected between high shear viscosity and the log body weight (Pearson $r = 0.129$; $p > 0.05$) and no species were clearly outstanding. Low shear viscosity (0.277 s^{-1}) versus log of body weight is shown in Fig. 3 for the same 27 species as in Fig. 2. It is obvious from this plot that, compared to high shear viscosity (Fig. 2), there is a wider range for low shear viscosity across different species. No significant correlation exists for the entire data set when including both the black and gray data points in Fig. 3 (Pearson $r = 0.250$, $p > 0.05$). However, careful inspection of Fig. 3 indicates that there is a group of 11 species positioned far below the main group, either because their low shear viscosity values are very much lower than expected for their body weight range or because their body weight is very large (i.e., elephant); the points for this group are shown in gray. Exclusion of data for these 11 species (i.e., considering only the black points) yields a highly significant correlation (Pearson $r = 0.751$, $p < 0.001$).

Allometric analysis of parameters reflecting the rheological behavior of RBC also revealed interesting relationships with body weight. As expected, the RBC aggregation versus body weight relationship exhibited a pattern similar to that for low shear rate blood viscosity (Fig. 4). Again, there are several species shown in gray with marked deviations from the pattern for the rest of the group. Not including these five species in the correlation analysis enhanced the Pearson r to 0.860 ($p < 0.0001$) from 0.506

Fig. 3. Whole blood viscosity measured at 0.277 s^{-1} for 27 mammalian species versus log body weight. The viscosity data were derived from Johnn et al. [20] and representative body weight data for each species was obtained from <http://genomics.senescence.info/>. Pearson r for the entire data set is 0.250 ($p > 0.05$), indicating a non-significant correlation. Correlation analysis including *only* the black data points yielded a Pearson $r = 0.751$ ($p < 0.0005$). The regression line represents only the black data points.

Fig. 4. Red blood cell aggregation indexes reported by various groups for 22 mammalian species versus log body weight. Aggregation data from Baskurt et al. [10] and representative body weight data from <http://genomics.senescence.info/>. Pearson r for the entire data set is 0.506 ($p < 0.05$), while including *only* the black data points gave a Pearson $r = 0.860$ ($p < 0.0001$). The regression line represents only the black data points.

($p < 0.05$) for all data points. Analysis of available comparative data for RBC deformability in terms of half-maximal shear stress also revealed a significant correlation with body weight (Fig. 5) although the correlation coefficient ($r = 0.743$) was not highly significant ($p < 0.05$).

The influence of body weight on hemorheological parameters can be further evaluated by comparing the exponential coefficients of regressions using a power function [19] (Table 1). It is obvious by comparing the exponential term of body weight that high shear viscosity has a relatively small dependence on body weight whereas low shear viscosity and RBC aggregation are influenced by body weight to a much greater extent. Furthermore, excluding species deviating from the main group (i.e., excluding the gray points in Figs. 3 and 4) markedly increased the power parameter, thus indicating that body weight is a more effective factor in these restricted groups; these observations are consistent with the discussions above related to correlation coefficients.

Fig. 5. Shear stress required to achieve one-half of maximum RBC deformation versus log body weight; an increase of this stress indicates reduced deformability. Shear stress data from Windberger and Baskurt et al. [37] and representative body weight data from <http://genomics.senescence.info/>. Pearson r for the data set is 0.743 ($p < 0.05$) thus indicating a significant correlation between RBC rigidity and log body weight.

Table 1

Allometric equations for hemorheological parameters. Data presented in Figs. 2–5 were used to calculate the equation parameters using a non-linear curve fitting algorithm. (see text for details, W is body weight, N is number of species)

Parameter	N	Equation	R^2
High shear viscosity (128.5 s^{-1})	27	$Y = 4.17 + W^{0.012}$	0.013
Low shear viscosity (0.277 s^{-1}) – entire group	27	$Y = 26.07 + W^{0.087}$	0.052
Low shear viscosity (0.277 s^{-1}) – selected species	16	$Y = 23.35 + W^{0.195}$	0.553
RBC aggregation – entire group	22	$Y = 18.30 + W^{0.095}$	0.146
RBC aggregation – selected species	17	$Y = 11.57 + W^{0.236}$	0.687
Half maximal shear stress	9	$Y = 3.01 + W^{0.140}$	0.589

4. Implications of allometric relations of hemorheological parameters

The allometric relations for hemorheological parameters summarized above may provide insight into the evolutionary processes of mammalian circulatory functions. That is, allometric relations might help understanding the regular patterns in the mammalian kingdom and providing answers to “why” questions about physiological features [16]. Additionally, species with traits markedly different from the main group may provide interesting evidence for specific adaptations [16]. While the flow properties of blood have not frequently been the subject of such investigations, studies in this area have the potential to initiate new discussions regarding the mammalian evolutionary processes and components of circulatory function [6]. A complete analysis of functional relationships of blood rheology and circulatory function across mammalian species and their evolutionary implications is beyond the scope of this review; the material below presents only a general discussion including several speculations.

The basic approach presented in Section 3 indicates: 1) a significant dependence of RBC aggregation on body weight as reflected by both low shear viscosity and RBC aggregation indexes, with the general trend indicating that the intensity of RBC aggregation increases with increased body size; 2) that RBC deformability has a lower degree of dependence on body weight.

4.1. Red blood cell aggregation – body weight relationship: What does it mean?

What might be the drive for the evolution of higher RBC aggregation intensity in species with larger body size? Obviously, the question can also be asked the other way: what is the advantage of having lower degrees of RBC aggregation for species with smaller body size? Certainly, such an evolution would be expected to be based on specific fitness advantages of the evolved trait [16]. Two hypotheses, in conflict with each other, can be proposed to explain such relationships between RBC aggregation and body size.

4.1.1. Body size, metabolic rate and red blood cell aggregation

It is generally accepted that the metabolic rate per unit body weight is significantly dependent on body size, with larger animals having a lower metabolic rate per unit body weight [22]. Thus, smaller mammals need higher oxygen transfer to their tissues and thus require more effective blood flow. Therefore, species with smaller body size may benefit from reduced RBC aggregation as it is the major determinant of blood viscosity at low shear rates, at least when measured under *ex vivo* conditions. Higher degrees of RBC aggregation may predict higher flow resistance, yet this may not be a limiting factor for adequate tissue perfusion in larger mammals due to their relatively lower demand for oxygen per unit weight of tissue. In brief, this hypothesis is based on the fitness advantage of reduced RBC aggregation in smaller mammals.

4.1.2. Blood vessel dimensions, axial accumulation and aggregation of red blood cells

It is now well recognized that the effects of RBC aggregation on flow dynamics in tubes (e.g., flow in blood vessels) may differ from those predicted based on *ex vivo* measurements [10]. The mechanisms contributing to this finding are mainly based on the promotion of RBC axial accumulation during tube flow and are discussed elsewhere in detail [2, 8]. Briefly, promotion of RBC axial accumulation by enhanced aggregation reduces the frictional resistance at the vessel wall and enhances hematocrit reduction in the microcirculation which, in turn, leads to lower *in vivo* flow resistance [2, 7]. However, RBC aggregation has a time constant comparable with the residence time of blood in vascular segments, and therefore the full development of axial migration and related hydrodynamic mechanisms require a sufficiently long, unbranched vascular segment [21]. Inasmuch as blood vessel lengths are increased with body size, the advantage of intense RBC aggregation and the consequent improvement of tissue perfusion might be more obvious in larger species. This hypothesis is thus based on the fitness advantage of enhanced RBC aggregation in larger mammals.

Obviously, the second hypothesis based on the necessity of a certain blood vessel length for improved fitness due to RBC aggregation may also explain the very low or absent aggregation in small-sized mammals as predicted by the allometric relation presented above Table 1, Fig. 4). Higher degrees of RBC aggregation may not result in any benefit in terms of reduced blood flow resistance if the animal does not have blood vessels long enough for fully-developed axial accumulation.

There is an additional line of evidence that seems contradictory to the hypothesis based on the negative impact of RBC aggregation on tissue perfusion. It has been shown that “athletic” species, as based on their maximal oxygen consumption, are characterized by higher degrees of RBC aggregation compared to sedentary species [25]. The “athletic” group includes horse, antelope and dog, animals that fit on the regression line in Fig. 4 for the allometric relation for RBC aggregation. Therefore, it can be assumed that natural selection favored high levels of aggregation in species which require large increases of tissue perfusion during their athletic activity.

Physiological reasoning related to edema formation suggests a possible advantage for the enhanced RBC aggregation in athletic animals. Capillary blood pressure is the main determinant of fluid movement

across the capillary wall, with this pressure a direct function of the “Pre” to “Post” capillary resistance ratio. During exercise, blood flow rate is increased due to the decrease of the Pre resistance (i.e., arteriolar dilation), thereby increasing capillary blood pressure, fluid movement into tissue space, and possible edema formation. However, if the Post resistance also decreases at the same time, both the elevation of capillary blood pressure and fluid movement into tissue are less. This decrease of Post resistance is related to the non-Newtonian, shear-thinning rheological behavior of blood that is enhanced by RBC aggregation: increased blood flow rate during exercise increases vascular shear rate and hence lowers blood viscosity and Post flow resistance. In the absence of RBC aggregation, blood would have nearly Newtonian flow behavior, Post resistance would be unaffected by flow rate, and capillary blood pressure would increase more than for blood where RBC aggregation can occur.

As mentioned above, the outliers of allometric relations may also provide insight into their evolutionary histories [27]: the interesting patterns in both Figs. 3 and 4 indicate that a number of species do not follow the general relation. These outliers are species with very low RBC aggregation or with low shear blood viscosity indicating very low aggregation. Excluding the elephant and whale that have extremely large body sizes, all other outlier species belong to the order Artiodactyla, including domestic cattle, goat and sheep; many of these species have lower maximal oxygen consumption and lower athletic capacity. Therefore, even though the relatively large body sizes of cattle, goat and sheep suggest they would have been suitable for the fitness advantage of intense RBC aggregation, selective pressure for the evolution of this trait was most likely lacking in their evolutionary environment.

Promislow [27] has noted that the order Artiodactyla has also been identified as an outlier of the allometric patterns for RBC size. It was suggested by Promislow that small RBC may have been selected for optimizing oxygen transfer in the evolutionary history of the order Artiodactyla since this evolution occurred in higher plateaus with lower oxygen partial pressure [23]. This alternative evolutionary adaptation might have suppressed the potential advantage of RBC aggregation, thus indicating the importance of evolutionary environment, including altitude and geography, in the selection of diverse “solutions for circulatory problems”. Traits of species are not “designed”, in the evolutionary sense, for perfection, but rather reflect the results of various trade-offs developed under various environmental constraints [16].

5. Conclusion

Evolutionary biology has become an important element of medical reasoning during the last several decades. Darwinian medicine has been applied to understanding the development of various health conditions, with consequences related to the management of these problems [16]; comparative physiology has been an important tool in developing the concepts of Darwinian medicine. Comparative studies of the flow properties of blood and the analytical reasoning based on the resulting data may yield new conceptual approaches to circulatory functions with possible clinical outcomes.

Unfortunately, comparative data for the rheological properties of blood and its formed elements are currently very limited. Various publications have reported hemorheological data on small groups of mammals [1, 3, 5, 24, 25, 30–33, 35, 36, 38] that are not usually selected to represent any phylogenetic relationship. Combining data from different studies may not always provide the best data set due to important differences of methodology. Many studies have been performed on animals in captivity and therefore might be criticized for not reflecting the natural environment of the species [27]. Carefully designed comparative investigations of hemorheological parameters, together with a number of hematological and physiological parameters, would contribute significantly to a better understanding of circulatory functions in the animal kingdom.

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