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Critical Focus

# The Hematocrit and Blood Viscosity are Modulated to Maintain Constant Wall Shear Stress in the Carotid Sinus

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## Abstract

Vascular wall shear stress must be within the physiologic range for normal blood flow, including preferential flow patterns and the maintenance of the antithrombotic phenotype of the endothelium. Wall shear stress varies with blood viscosity. The hematocrit, i.e., the volume percent of blood comprised of erythrocytes, is a strong determinant of blood viscosity, wall shear stress, cardiac work and oxygen transport. We hypothesize that in humans the hematocrit is modulated to maintain constant wall shear stress in the carotid sinus, a dilatation of the internal carotid artery that is tailored to detect wall shear stress. These data modulate the renin-angiotensin-aldosterone system, including the concentration of erythropoietin, the hormone that controls erythrocyte production. Using previously published data, we show that the different blood viscosities and carotid diameters in the sexes combine so that wall shear stress is virtually identical in both. Maintaining normal wall shear stress may explain the increasing hematocrit with growth and sports anemia, a mild dilutional anemia in some exceptionally fit athletes. Previously, these phenomena were poorly understood because of the assumption that the hematocrit is determined by the need to maximize oxygen transport. We term this the "reductionist" view. This view was reinforced historically by overestimation of tissue oxygen needs. Identification of additional complexity makes a holistic approach, examining an entire system rather than its parts, more attractive. The authors argue that a holistic approach is necessary for understanding what determines the hematocrit, explaining the sex difference in hematocrit, the increasing hematocrit with growth, and sports anemia.

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## INTRODUCTION

The hematocrit is the volume percent of blood composed of red blood cells or erythrocytes. It closely correlates with the concentration of hemoglobin. The hematocrit is the strongest intrinsic determinant of blood viscosity and, therefore, is a determinant of blood flow, vascular resistance, cardiac work, and oxygen ($O_2$) transport. An increase in blood viscosity causes a threefold inverse change in blood flow in vivo [1], reducing the delivery of $O_2$, glucose, and all other solutes.

Three values of hematocrit are recognized: normal, native, and optimal. The normal hematocrit is usually defined as any value that falls within two standard deviations of the mean of a population of apparently healthy people. In one laboratory the normal range is 38.3–48.6% in males and 35.5–44.9% in females.[1] The native hematocrit is the stable value in one individual. It may be outside of the normal range in several non-hematologic diseases. We believe that in those instances the native hematocrit results from a homeostatic response to normalize blood viscosity and is not pathologic for that individual [2]. The native hematocrit should be distinguished from an abnormal value due to a nutritional deficiency or hematologic disease.

Finally, the optimal hematocrit is the theoretical value that maximizes $O_2$ transportation. The optimal hematocrit has historically been viewed as solely a function of blood [3]. Until very recently, the specific impact of cardiac power on $O_2$ transport had not been studied (vide infra).

[1] https://www.mayoclinic.org/tests-procedures/hematocrit/about/pac-20384728

Of the three values, only the normal hematocrit is fully understood. The uncertainty surrounding the other values is due to the belief that the hematocrit is determined solely by $O_2$ demand. In previous work [2], two of the authors argued that the hematocrit in humans is modulated to maintain blood viscosity. In that work, we described the systemic vascular resistance response, a physiological response that normalizes systemic vascular resistance by reducing the hematocrit. In this response, increased systemic vascular resistance is detected by the stretching of mechanoreceptors in the left ventricle.

It has recently been shown that additional information to modulate blood viscosity is collected by endothelial mechanoreceptors in the carotid sinus, a dilatation of the proximal internal carotid artery in humans (Figure 1). The unique anatomy of the carotid sinus allows the collection of information that contributes to the robust control of blood viscosity. These mechanoreceptors detect wall shear stress [4,5], and this information is used to increase the hematocrit and blood viscosity by upregulating the activity of the renin-angiotensin-aldosterone system (RAAS).

In this paper, we use data from the literature to show that wall shear stress in the carotid sinus is similar in both sexes despite differences in vascular diameter, hematocrit, blood viscosity and cardiac power. The hematocrit is an independent variable that determines blood viscosity and the dependent variable wall shear stress. Cardiac power is another independent variable because it contributes to the shear rate of arterial blood, which, along with blood viscosity, determines wall shear stress.

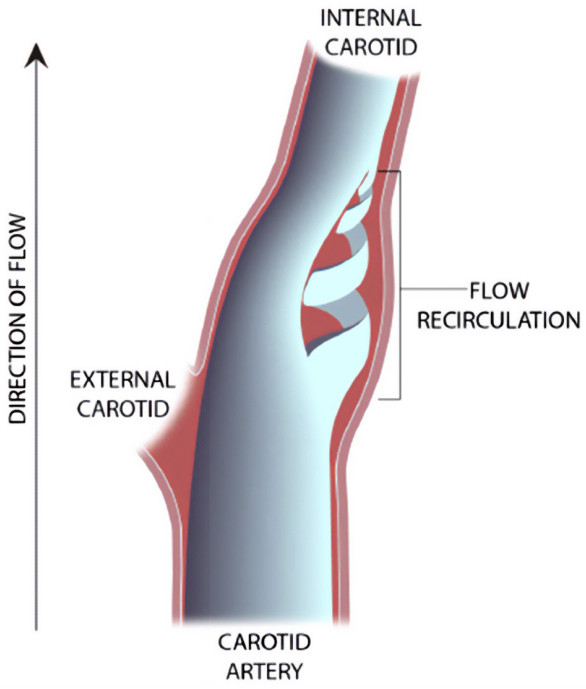


**Figure 1: Flow recirculation in the carotid sinus.** During high velocity systolic flow, an area of flow recirculation develops in the carotid sinus. This occurs because of the high value of Reynolds number and the change in arterial geometry due to the dilatation of the carotid sinus. Modified from reference [5]. **doi:**10.5048/BIO-C.2024.2.f1

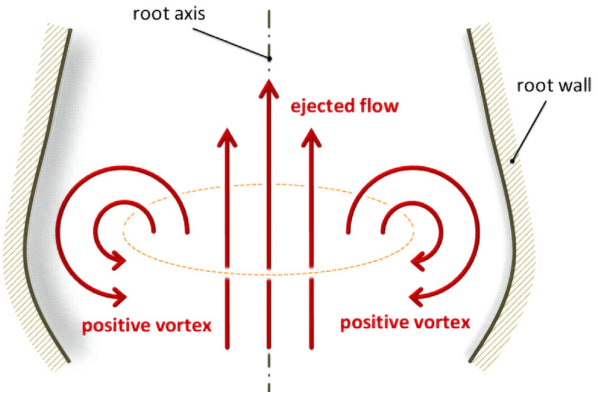


**Figure 2: Vortices in the sinuses of Valsalva in the root of the aorta.** These develop during systole and close the aortic valve at the end of systole. From reference [10]. **doi:**10.5048/BIO-C.2024.2.f2

In addition to explaining the sex difference in normal hematocrit, we use this insight to explain the increasing hematocrit with growth and sports anemia, a dilutional anemia seen in some extremely fit athletes. In these conditions, changing cardiac power requires changes in hematocrit and blood viscosity to maintain wall shear stress in the carotid sinus. It is possible that these phenomena have been unexplained or even unexamined because the biophysical impact of blood has been underappreciated given the obvious and vital role of hemoglobin in transporting oxygen. However, a critical examination of the different hematocrits in the sexes, the increasing hematocrit with growth and sports anemia reveals they are better explained by maintaining normal wall shear stress, not oxygen delivery.

## The milieu intérieur

Blood viscosity must be under homeostatic control for a variety of very important reasons. Pathologically high blood viscosity decreases tissue perfusion, increases the risk of thrombosis, and increases cardiac work [6]. Pathologically low blood viscosity wastes cardiac power by fostering turbulence. Turbulence also activates white blood cells and platelets and damages erythrocytes. This causes hemolysis. Free hemoglobin in the blood is toxic to the kidneys [7]. If blood viscosity is low enough, a vicious cycle can develop: low blood viscosity causes hemolysis, which reduces the hematocrit and blood viscosity further, worsening hemolysis, and so on. This results in a condition called high-output cardiac failure, which can be life-threatening [8].

Physiologic blood flow and wall shear stress require normal blood viscosity. One manifestation of normal blood flow and viscosity is the physiologically useful streamlines that form during systole called "preferential flow patterns" [9]. In humans, these include the vortices in the sinuses of Valsalva that close the aortic valve during diastole (shown in Figure 2) [10], the streamlines at the apex of the left ventricle and flow recirculation in the carotid sinus [9,5]. Experience with artificial heart valves demonstrates that preferential flow patterns are very sensitive to flow conditions [9,10]. It has recently been shown that the abnormally elevated blood viscosity that accompanies

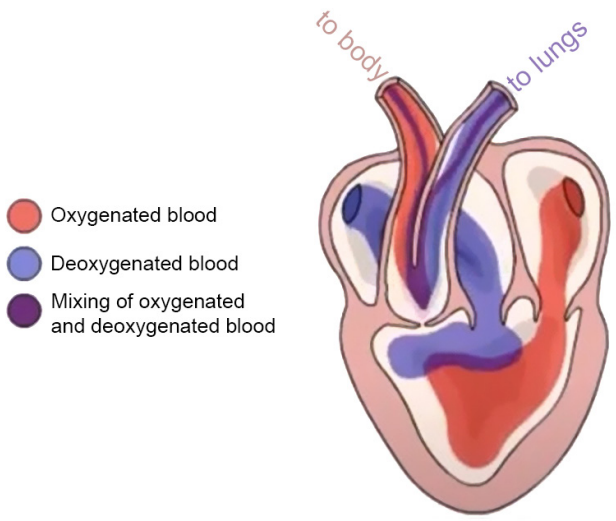


**Figure 3: Preferential blood flow in the frog heart.** Normal cardiac anatomy, power and blood viscosity create preferential patterns of blood flow that allow relative separation of oxygenated from deoxygenated blood when blood viscosity and anatomy are normal. Used by permission of iWorx Systems, Inc. **doi:**10.5048/BIO-C.2024.2.f3

acute coronavirus disease 2019 (COVID-19) causes the loss of cardiac preferential flow patterns [11].

Figure 3 shows the preferential flow patterns in the single ventricle of the frog heart that allow the relative separation of deoxygenated and oxygenated blood. If blood viscosity is too low, the velocity and momentum of blood will be too high. This will alter streamlines so that they overshoot their intended targets, increasing the mixing of oxygenated and deoxygenated blood. High blood viscosity will also increase the mixing of oxygenated and deoxygenated blood because it decreases ventricular filling. This decreases the physical separation of the ventricular apex, which contains blood with a relatively high oxygen concentration, and the more proximal ventricle, which contains relatively deoxygenated blood.

These observations demonstrate the fundamental importance of normal blood viscosity in homeostasis. Blood viscosity is part of what the eminent physiologist Claude Bernard called the "milieu intérieur."

## The carotid sinus

The shape of the carotid sinus creates a region of flow circulation against the sinus wall. This has been shown using ultrasound and both physical and virtual models [5,12]. The amplitude of wall shear stress is increased in this region. Thus, the shape of the sinus results in "gain" in electrical engineering terms [5]. This is another example of preferential blood flow.

The carotid sinus is tailored to detect changes in wall shear stress not in blood pressure as previously thought. This has been called the "viscometer" function of the carotid sinus. It provides unique information, rather than a duplicate of the information collected by baroreceptors in the aortic arch. Via the glossopharyngeal nerve, information from the carotid sinus goes to the nucleus/tractus solitarius in the medulla oblongata in the central nervous system. This information is processed via multiple interneurons and influences the autonomic control of the RAAS [13]. Angiotensin II, a significant effector of the RAAS, increases red blood cell mass by acting as a growth factor for erythroid progenitor cells and as a secretagogue for erythropoietin, the hormone that controls erythrocyte production [14]. Thus, the RAAS increases the hematocrit and blood viscosity. It is the physiologic antagonist of the systemic vascular resistance response.

## Microvascular wall shear stress

Shear stress at a blood vessel wall is defined by Equation (1):

$$\tau_w \equiv \tau(y=0) = \mu \frac{\partial u}{\partial y}\Big|_{y=0} \quad (1)$$

where $\tau_w$ is wall shear stress, $y$ is the distance from the blood vessel wall, $\mu$ is dynamic viscosity, $u$ is the flow velocity. Thus, wall shear stress is the product of blood viscosity ($\mu$) and the rate of change of flow velocity. At the vessel wall, shear stress is directly related to blood velocity. If wall shear stress is to remain constant, an increase in either blood viscosity ($\mu$) or the rate of change of flow velocity ($\partial u/\partial y$), requires an equivalent decrease in the other factor.

In the microvasculature, wall shear stress is controlled by modulating vascular diameter. If flow is constant, an increase in vascular diameter decreases blood velocity and wall shear stress. Microvascular diameter is controlled in part by endothelial production of nitric oxide (NO) and prostaglandins. The synthesis and release of these molecules are modulated by local wall shear stress in the physiologic range. This was shown in experiments in which vascular diameter changed in response to changes in perfusate velocity and viscosity so that the calculated wall shear stress remained near control values [15].

Gross, large-scale control of wall shear stress allows blood to be delivered by conducting and distributing arteries at physiologic shear stresses so that only fine-tuning of local blood flow is necessary in the microvasculature. Modulating vascular diameter to control flow is effective in the microvasculature because a change in the diameter of vessels with a diameter less than 0.3 mm causes a relatively large change in the vascular cross-section when compared to the same absolute change in the diameter of a large artery. Nitric oxide is not suitable for broad, large-scale control of wall shear stress because of its extremely short half-life (roughly 2 milliseconds intravascularly) [16], its high cost to synthesize (a molecule of arginine and NADPH), and its toxicity (it binds to all metalloproteins, including hemoglobin and cytochrome oxidases).

Instead, wall shear stress in conducting arteries is controlled by changes in blood viscosity and arterial blood velocity, as indicated in Equation (1). Cardiac power and systemic vascular resistance are important in determining blood velocity. When cardiac power and vascular diameter change with growth or training, the hematocrit must be modulated to maintain blood viscosity and wall shear stress in large arteries.

### Sex-specific Hematocrits

Explaining the different normal hematocrits in the sexes in humans has stimulated only limited interest, perhaps because a superficial analysis suggests it could be attributed to different $O_2$ requirements and different set points for hematocrit based on lean body mass. The sex difference in normal hematocrits was reviewed by Murphy [17].

The concentration of erythropoietin is similar in both sexes. To explain the sex difference in hematocrits Murphy proposed that estrogen dilates the microvasculature and that the hematocrit in these vessels is higher in females. A larger concentration of erythrocytes in the microvasculature would result in a lower hematocrit in peripheral veins, the ones that are ordinarily sampled. He noted that this proposal requires that the Fåhræus effect—the decrease in hematocrit with decreasing diameter in arterioles less than 0.3 mm—acts differently in the sexes and that the mean diameter of the microvasculature is larger in females than in males. This speculation has not been confirmed. This proposal does not explain what determines the putative set points for normal hematocrit.

An unnecessarily high hemoglobin concentration and hematocrit would theoretically decrease the fitness of an organism by increasing cardiac work and energy expenditure. However, if only the tissue $O_2$ requirement is considered, hemoglobin is present in excess in both sexes [17]. This is easily shown by asymptomatic anemia, a common condition. The minimum hematocrit for survival, based on observations of adult surgery patients who refused transfusion, is approximately 18% [17]. The hematocrit at which anemia becomes symptomatic is obviously much higher than this minimum.

An alternative explanation for the sex difference in hematocrits and blood viscosity is that these are modulated to normalize wall shear stress in the carotid sinus. A higher hematocrit and blood viscosity are necessary in the male to maintain normal wall shear stress given the greater cardiac power of the male heart. Peak cardiac power output ranged from 3.11 to 7.94 W in males and 2.53 to 5.57 W in females in one study [18].

## RESULTS

### Wall shear stress is similar in the sexes

Mean peak arterial blood velocity in the common carotid is statistically similar in the two sexes [19,20]. In one study, peak common carotid artery blood velocity was 62.7 ± 2.5 cm/s in the right common carotid artery and 63.9 ± 2.0 cm/s in the left common carotid [20]. Therefore, a difference in the rate of change of flow velocity at the carotid vascular wall is due to differences in lumen diameter (Figure 4). At a vessel wall, $\partial u/\partial y$ varies inversely with lumen diameter.

From Equation (1) and the reasoning put forth above, the product of blood viscosity and the inverse of the vascular diameter should be equal if wall shear stress is the same in both sexes, as in Equation (2).

$$\mu_{female} \cdot \frac{1}{vascular\ diameter_{female}} = \mu_{male} \cdot \frac{1}{vascular\ diameter_{male}} \quad (2)$$

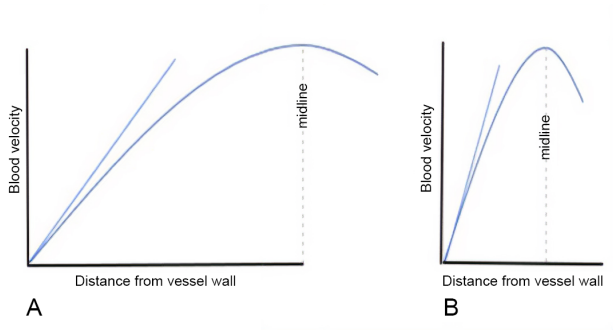


**Figure 4: The effect of vascular diameter on δu, the rate of change of blood velocity.** The fully developed velocity profile in laminar flow is parabolic. The arterial velocity profile in a large (panel A) and small vessel (panel B) is represented by the two parabolas. Neither parabola is shown completely. Peak blood velocity, represented by the height of the parabola, is the same in both parabolas. The base of each parabola is representative of the diameter of the blood vessel. The base of the parabola in panel A is larger than that in B. The tangential line in each panel represents *δu* at a blood vessel wall. At the vessel wall, *δu* is inversely related to the vessel diameter. **doi:**10.5048/BIO-C.2024.2.f4

At a high shear rate of 100/s, blood viscosity in males is 3.43 ± 0.33 centipoise (cP) and 3.20 ± 0.49 cP in females [21]. The lumen diameter of the left distal common carotid artery is 11.03 ± 1.28 mm in males and 10.25 ± 1.39 mm in females. The lumen diameter of the distal right common carotid artery is 11.65 ± 1.37 mm in males and 10.71 ± 1.23 mm in females. The lumen diameter of the left carotid sinus is 10.96 mm in males and 10.32 mm in females. The lumen diameter of the right carotid sinus is 11.29 mm in males and 10.54 mm in females [22].

Wall shear stress can be calculated and compared using Equation 2. In the left distal common carotid artery:

$$3.20 \cdot \frac{1}{10.25} = 3.43 \cdot \frac{1}{11.03}$$
$$0.31 = 0.31$$

In the right distal common carotid artery:

$$3.20 \cdot \frac{1}{10.71} = 3.43 \cdot \frac{1}{11.65}$$
$$0.30 \approx 0.29$$

In the left carotid sinus:

$$3.20 \cdot \frac{1}{10.32} = 3.43 \cdot \frac{1}{10.96}$$
$$0.31 = 0.31$$

In the right carotid sinus:

$$3.20 \cdot \frac{1}{10.54} = 3.43 \cdot \frac{1}{11.29}$$
$$0.30 = 0.30$$

Table 1 summarizes the preceding data. This analysis suggests that blood viscosity is modulated to maintain wall shear

**Table 1: Data used in calculating sex-specific values of the product of blood viscosity and inverse of vascular diameter.** Data are expressed as the mean ± standard deviation. Abbreviations: W: watts; cP: centipoise; Lt: left; CCA: common carotid artery; mm: millimeters; Rt: right; CS: carotid sinus; μ: blood viscosity; N.A.: not applicable.

| Parameter | Male | Female | Reference |
|---|---|---|---|
| Peak cardiac power output (range) | 3.11–7.94 W | 2.53–5.57 W | 18 |
| Normalized Blood viscosity at 100s-1 | 3.43 ± 0.33 cP | 3.20 ± 0.49 cP | 21 |
| Lt CCA lumen diameter | 11.03 ± 1.28 mm | 10.25 ± 1.39 mm | 22 |
| Rt CCA lumen diameter | 11.65 ± 1.37 mm | 10.71 ± 1.23 mm | 22 |
| Lt CS bulge lumen diameter | 10.96 ± 2.23 mm | 10.32 ± 1.89 mm | 22 |
| Rt CS bulge lumen diameter | 11.29 ± 2.18 mm | 10.54 ± 1.80 mm | 22 |
| μ • 1/ Lt CCA diameter | 0.31 | 0.31 | N.A. |
| μ • 1/ Rt CCA diameter | 0.29 | 0.30 | N.A. |
| μ • 1/ Lt CS bulge diameter | 0.31 | 0.31 | N.A. |
| μ • 1/ Rt CS bulge diameter | 0.30 | 0.30 | N.A. |

stress in the carotid sinus and the higher blood viscosity and hematocrit in males is a homeostatic phenomenon to maintain normal wall shear stress. The fact that peak common carotid artery blood velocity is statistically similar in both sexes despite the larger vessels and greater power of the male heart also suggests that carotid sinus wall shear stress is conserved, given the powerful effect of blood velocity on wall shear rate.

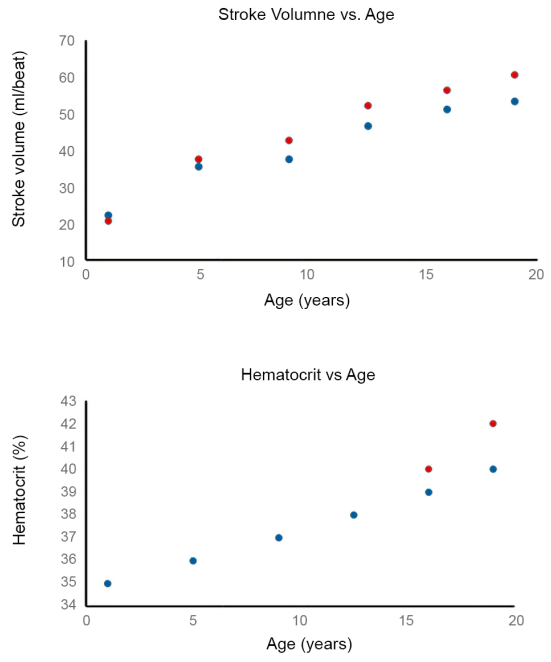


**Figure 5: The relationships of stroke volume and hematocrit (a surrogate marker for blood viscosity) to age.** Values of hematocrit are from the literature [25]. Stroke volume was calculated using the formulae stroke volume = 22.2 • age$^{0.30}$ in females and 20.85 • age$^{0.36}$ in males [26]. When two values are present at one age, the red value is present in males. **doi:**10.5048/BIO-C.2024.2.f5

## The increasing hematocrit in growth

The cause of the increasing hematocrit with growth in humans has not been addressed to the authors' knowledge, possibly because it also could conceivably be attributed to an increasing $O_2$ requirement. Production of a factor induced by hypoxia is unlikely to be the stimulus for the increasing hematocrit with growth. If that were the case, growth would be characterized by cyclical episodes of hypoxia followed by an increase in hematocrit sufficient to relieve hypoxia. However, the hemoglobin concentration in children is also higher than necessary to meet $O_2$ needs [17]. Mild anemia, as seen in certain congenital hemolytic anemias such as hereditary spherocytosis, is compatible with normal growth. When these anemias are caused by decreased erythrocyte deformability (which increases blood viscosity), the anemia is a homeostatic response caused by the systemic vascular resistance response to normalize systemic vascular resistance [2].

Instead of being driven by increasing $O_2$ needs, we believe the increasing hematocrit with growth serves to maintain wall shear stress in the carotid sinus. The combination of increasing cardiac power due to growth of the heart and decreasing vascular resistance due to both increasing vascular diameter and the larger number of blood vessels with growth would cause high-output heart failure without a corresponding increase in systemic vascular resistance provided by increasing blood viscosity. High-output heart failure develops with an extreme mismatch between cardiac power and systemic vascular resistance [23,24]. Systemic vasoconstriction occurs but does not prevent the condition.

Figure 5 shows the relationship between hematocrit [25] and stroke volume [26] with increasing age. The hematocrit is used as a surrogate for blood viscosity and stroke volume is a surrogate for cardiac power because of a lack of data in the pediatric age group. Both show continuous increases from infancy to adulthood.

### Sports anemia

Sports anemia is a dilutional anemia seen in some exceptionally fit athletes. In this condition, plasma volume is increased disproportionately to red blood cell mass. The counterintuitive nature of "sports anemia" has inspired a small literature but produced no explanation.

Studies have shown that chronic exercise and improved fitness decrease systemic vascular resistance by 7.1%, increase stroke volume by 15.4%, and increase left ventricular mass by 17% [27,28]. These changes increase cardiac power, peak arterial blood velocity and shear rate ($\partial u/\partial y$). These changes also require a decrease in blood viscosity to maintain wall shear stress within normal limits. Dilutional anemia is also seen in successful pregnancies [29]. Sports anemia should be viewed as an adaptive response that maximizes $O_2$ and glucose delivery by normalizing wall shear stress.

## DISCUSSION

One might argue that a hemoglobin concentration greater than necessary for tissue oxygen demands improves survivability after trauma and is a sufficient explanation for a putative setpoint that provides for such a hemoglobin concentration. The native hematocrit, the sex difference in hematocrit, the increasing hematocrit with growth and sports anemia argue strongly that there is no set point for the hemoglobin concentration. Instead, the hemoglobin concentration and hematocrit are governed by the setpoints for hemodynamic factors, wall shear stress, systemic vascular resistance and shear rate (vide infra). The hemoglobin content above that needed for $O_2$ transport is present to provide viscosity. Hemoglobin has both viscogenic (viscosity-producing) and $O_2$-transporting functions.

Normally, $O_2$ transport is not an important factor in determining the hemoglobin concentration or hematocrit. However, hypoxemia is a factor in inhabitants of high altitudes, severe chronic lung disease, and cyanotic congenital heart disease. Exercise tolerance is improved in cyanotic congenital heart disease patients with a hematocrit above 65% compared to those with a lower hematocrit [30]. The diameter of the epicardial coronary arteries is increased in cyanotic congenital heart disease [31], which decreases $\delta u$ and wall shear stress.

### Progress in understanding the hematocrit

Reductionism is the view that an organism can be understood by studying its components in isolation. In this paper, the reductionist view of the hematocrit is defined as the belief that the hematocrit is determined solely or predominantly by tissue $O_2$ needs. This view is seen in an editorial published in the *New England Journal of Medicine* in 2006 about correcting the low native hematocrit in renal failure patients which results from the systemic vascular resistance response [32]:

Why doesn't complete correction of anemia favor better cardiovascular outcomes in randomized, controlled trials? A higher hematocrit level should improve oxygen delivery to tissues. Indeed, tissue hypoxia and oxidative stress, as seen in patients with anemia, are both linked to inflammation and the progression of chronic kidney disease. However, complete correction of anemia might increase both blood pressure and the risk of thrombosis and accentuate vasoconstriction.

In this view, the impact of the hemoglobin concentration on factors other than $O_2$ transport, such as blood viscosity or wall shear stress, are given secondary importance. The historic view of the hematocrit is now known to have overestimated tissue $O_2$ needs. The current recommendation is that a transfusion trigger of 7–8 g/dL is adequate for most patients.[2] Further, it is now clear that complete correction of anemia may lead to excess morbidity and mortality because anemia often should be considered as a physiologically necessary adaptation in order to avoid hyperviscosity [6].

## CONCLUSION

Underestimation of the biophysical impact of the hematocrit, and thus blood viscosity, is a common mistake. Spivak drew attention to this problem over a decade ago in *The New England Journal of Medicine* [33]: "In the genomic era, readers may question attention given to a measurement as mundane as the hematocrit….Remarkably, despite the negative effect of erythrocytosis on all components of Virchow's triad (stasis of blood flow, hypercoagulability owing to platelet activation, and endothelial injury), the role of phlebotomy in the management of polycythemia vera is controversial…. The major reason for controversy, though, was a failure to consider certain principles of blood-volume physiology…. as the hematocrit rises above 45%, whole-blood viscosity increases above normal."

A link between the reductionist view of the hematocrit and Darwinism is seen in this quote from Dr. James Jandl's classic textbook *Blood* (1996): "That $O_2$ flow at high rates of shear is maximal at physiologic levels of hematocrit reaffirms the splendor of natural selection [3]." In his view, the normal and optimal values of hematocrit are identical. This view is relatively sophisticated in that it acknowledges the impact of blood viscosity on blood flow.

However, maximizing $O_2$ transport cannot explain why a healthy female might have a native hematocrit of 38%, which is within the normal female range but delivers less $O_2$ than a higher hematocrit would, or the elevated hematocrit in patients with cyanotic congenital heart disease, which should be selected against because of increased blood viscosity.

Reductionism is suitable for establishing a preliminary understanding of a biological process but is not sufficient for a deeper understanding. As the science journalist Diederick van der Hoeven wrote in 2019, "It is as if we had to understand the simplest situations first, before we could acquire a deeper insight into the complex mechanism of living nature".[3]

That deeper insight requires a holistic approach. Holism is the view that full understanding of a system requires analyzing

[2] https://www.the-hospitalist.org/hospitalist/article/125662/what-are-indications-blood-transfusion

[3] https://www.biobasedpress.eu/2019/09/reductionism-and-holism-in-the-life-sciences/#:~:text=Science%20rests%20on%20reductionism%3A%20the,be%20understood%20from%20the%20whole

its components while they are acting in concert. The heart, blood vessels and blood are seen as an integrated unit. Holism is necessary to understand complex quantities—such as blood pressure, systemic vascular resistance and endothelial wall shear stress—which arise from the interaction of the heart, blood vessels and blood. Holism recognizes "emergent phenomena," i.e., quantities that are fully expressed when the components of a system interact. Blood viscosity is an emergent phenomenon: the cumulative result of hematocrit, shear rate, erythrocyte deformability, zeta potential, osmolarity, and the size, shape, charge, and concentration of every plasma protein.

In the holistic view, $O_2$ transport is seen as a physical process determined by the hematocrit and cardiac output, which are determined by numerous biophysical variables including blood viscosity, cardiac power, and systemic vascular resistance. Consistent with this, a recent mathematical analysis concluded that the optimal hematocrit is higher than the normal hematocrit when constrained by cardiac power [34].

This helps explain the athletic success of Eero Mäntyranta. He was a Finnish cross-country skier who won several Olympic gold medals and World Championships. Because of a mutation in the gene encoding the erythropoietin receptor, he had a native hematocrit in the 60%s. It is possible that because of training he had exceptional cardiac power, which allowed him to exploit the increased $O_2$-carrying capacity of a higher hematocrit. Persons with this mutation can suffer from symptomatic hyperviscosity that requires medical attention. Mäntyranta died at age 76 of myocardial infarction [35].

The progress in understanding the hematocrit can be viewed as a case study in how the accumulation of knowledge necessitates the progression from a reductionist to a holistic view in a physiologic system. Understanding of the immune, endocrine, and nervous systems already have benefitted from the same progression. The progression from the reductionist to a holistic view of the hematocrit has been hampered by the unfamiliarity of physicians with the concepts of turbulence, non-Newtonian fluids, shear stress, and shear rate. The concept of viscosity may be intuitive and is reinforced by the ubiquity of motor oil which is classified by viscosity. However, physicians must be introduced to those other concepts in undergraduate physics or physiology courses or medical physiology in undergraduate medical education at the latest to understand critical phenomena such as the viscometer function of the carotid sinus, the systemic vascular resistance response, endothelial production of nitric oxide and prostaglandins, among others. Many of our earlier papers review these concepts by necessity [6,9].

The key insight contained in this paper is that wall shear stress is maintained in *Homo sapiens* by modulating the hematocrit, and thus, blood viscosity. This insight was made possible by the recent description of the "viscometer function" of the carotid sinus. Maintaining normal wall shear stress in the carotid sinus explains the sex difference in normal hematocrit, the increasing hematocrit with growth, and the heretofore poorly understood condition called "sports anemia." It also explains the differences between the normal, native, and optimal hematocrits. This insight is an example of the potential of the holistic or systems biology approach to understanding biology.

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