Antarctic fishes: experiments of nature which demonstrate the fundamental importance of blood viscosity

Abstract: Viscosity increases with decreased temperature. The author argues that loss of hemoglobin is a “disaptation” or evolutionary loss of function which confers a competitive advantage in Antarctic waters because of decreased blood viscosity. Because the likelihood of developing turbulent flow is inversely related to viscosity, a minimum degree of blood viscosity is necessary. Also, pathologically high shear caused by insufficient viscosity will activate or damage the formed elements of blood such as leukocytes and platelets. The necessary viscosity in icefish is provided by antifreeze glycoproteins.

Blood viscosity increases markedly with decreasing temperature. The viscosity of human blood at a normal hematocrit, 40%, at 0⁰ C was 16.7 cP at the high shear rate of 125/s in one study [1]. This is incompatible with life. Normal human blood viscosity at high shear rates is <4 cP. In Antarctic waters, which have a year-round temperature of ≈ -1.0⁰ C, minimizing blood viscosity has been the driving force in determining the dominant fish species. Blood viscosity in Antarctic fish is necessarily increased by the high concentration of antifreeze glycoproteins (AFGPs) required to prevent tissue freezing. Concentrations of AFGPs are typically 3.0 -3.5 g/dl [2] which make up the bulk of plasma protein in these animals [3].

Minimizing blood viscosity is essential to survive in Antarctic waters. One strategy to minimize blood viscosity is seen in the bald notothen, *Pagothenia borchgrevinki* (=*Trematomas borchgrevinki*). Blood viscosity in this fish is minimized because a substantial proportion of its erythrocytes are sequestered in the spleen at rest and released into the vasculature to meet metabolic demands. Brijs and colleagues studied the role of the spleen in these fish on hematocrit, aerobic capacity, cardiac work, and exercise tolerance by ligating the splenic vasculature in study animals, rendering them functionally asplenic. The hematocrit in sham-operated fish increased from 15.3±2.0% at rest to 25.9 ±1.1% after forced exercise, and oxygen carrying capacity increased 207%. The increased hematocrit and blood viscosity caused a 30% increase in cardiac workload and 12% increase in ventral aortic blood pressure. Hematocrit explained 50% of variability in blood pressure [4].

Functionally asplenic fish were unable to complete an exercise routine and fatigued twice as fast as sham-operated fish. These fish can produce a graded response so that fed resting fish had a higher hematocrit than unfed resting fish. In a related Antarctic fish, the emerald rockcod, *Pagothenia bernacchii* (= *Trematomus bernacchii*), blood viscosity increased from 4.37 cP to 6.79 cP after stress, measured at 225/s [5]. Hematocrit increased from 7.6% to 15.4%.

An even more extreme adaptation to minimize blood viscosity is present in Antarctic icefish, family Channicthyidae. Icefish blood lacks hemoglobin and its hematocrit is more accurately described as a “leukocrit.” Oxygen demand is decreased in this fish because its blood circulates at low pressure. This is possible because the cross-sectional area of its capillaries is two to three times greater than other bony fish, resulting in low peripheral resistance [6]. In one study, the blood viscosity of the crocodile icefish, *Chionodraco kathleenae* (= *C. hamatus*), leukocrit of 1.2% ± 0.82%, was 3.57 ± 0.21 cP at a high shear rate, 225/s [5].

A high output, high flow rate circulation with low resistance [7] could be prone to turbulence. The tendency to develop turbulence is determined by Reynolds number, *Re.* Reynolds number is described by the equation *Re*=*ρυD*/*μ*, where *ρ* is the density of the fluid, *υ* is the fluid velocity, *D* is the tube diameter, and *μ* is the fluid viscosity. The larger the value of *Re*, the more likely is turbulence to develop. Because blood viscosity is inversely proportional to *Re*, an adequate level of blood viscosity will decrease the tendency for turbulence. Turbulent blood flow damages the formed elements in blood such as leukocytes and platelets, increases resistance to flow, and wastes energy.

The dampening effect of viscosity on the development of turbulence was shown by Kameneva et al. [8]. Those investigators pumped an erythrocyte suspension through a closed loop at a constant hematocrit while varying viscosity by adding Dextran, a long chain polysaccharide thickening agent [9]. Flow was turbulent at the low viscosity, 2.0 ± 0.1 cP and laminar at the high viscosity, 6.3 ± 0.1 cP. After 90 minutes, hemolysis was greater with turbulent flow. The mechanism by which turbulent flow causes hemolysis is under active investigation because hemolysis is a complication of using mechanical devices in cardiopulmonary bypass and extracorporeal membrane oxygenation (ECMO).

The blood viscosity of the crocodile icefish and resting emerald rockcod at high shear rates is comparable to humans despite their lower hematocrits and lower body temperature. This suggests that there could be an optimal viscosity which maximizes the function of blood, transport of solutes and essential formed elements (platelets and leukocytes). Blood viscosity in icefish is determined largely by the plasma concentration of antifreeze glycoproteins (AFGPs). These are a family of eight polymers of a glycosylated tripeptide encoded by separate genes which vary in molecular weight from 2,600 to 33,000 Da [3].

Typically, the thermal hysteresis (antifreeze) activity of AFGPs is proportional to their molecular weight [10]. However, large molecules increase plasma viscosity more than smaller ones [11]. Thus, it is the relative expression of higher and lower weight AFGPs which determines blood viscosity in these fish. In an example of parsimony, AFGPs act as both antifreeze and thickening agents.

Harding et al. reported that 25% of AFGPs are high molecular weight and 75% are lower molecular weight isoforms in the bald notothen and the Antarctic toothfish (*Dissostichus mawsoni)*, another notothenioid [3]. This pattern of isoform expression favors a lower blood viscosity over maximal prevention of ice formation. Presumably, expression AFGPs can be modified in response to a challenge to homeostasis. This could be important in icefish because the slope of the temperature-blood viscosity curve is steep between 0o C and -1.8o C [5].

Mammals have a mechanism to control blood viscosity, the systemic vascular resistance response [12]. Elevated blood viscosity increases vascular resistance which is sensed by mechanoreceptors in the left ventricle. To maintain normal systemic vascular resistance, cardiomyocytes express B-type natriuretic peptide, which causes vasodilation and natriuresis. Concurrently, red blood cell mass is decreased by multiple mechanisms in order to maintain a constant hematocrit, the strongest determinant of blood viscosity.

Acutely, red cell mass is decreased by splenic hemophagocytosis and production of soluble erythropoietin receptor. This is a truncated version of the erythropoietin receptor which lacks the transmembrane and intracellular domains. This molecule decreases erythropoiesis by binding to circulating erythropoietin before it can act in the bone marrow. Control of cytokine activity by such “decoy receptors” is a common motif in Class I cytokine receptors [12]. Decreased transcription of the erythropoietin gene chronically decreases red cell mass [13]. Coordinated decreases in intravascular volume and red cell mass are necessary to maintain hematocrit, which is the strongest determinant of blood viscosity in mammals.

Mechanoreceptors are present in the icefish heart [6]. The gene for BNP is highly conserved in bony fish, including the crocodile icefish [14]. The erythropoietin receptor is expressed in the adult zebrafish heart [15]. Thus, it is possible that a mechanism similar to the systemic vascular resistance response is active in icefish and controls blood viscosity by modulating expression of AFGP isoforms.

A hemoglobin-less animal like the icefish would have been an opportunity to test the adaptive value of extremely low-viscosity blood. Blood of lower viscosity would require less energy to pump from the heart. The data of Kameneva et al. show that the proper blood viscosity has adaptive value by limiting shear-mediated damage to formed elements within blood, and explains why the blood viscosity of the icefish at high shear rates is comparable to humans.

Like all fluids, viscosity is a fundamental property of blood as a material and must be present in proper measure for its optimal function, transporting solutes and formed elements. In this way, the viscosity of blood is like the compression strength of bone, yield strength of tendons, and elasticity of arteries. Antarctic fish are experiments of nature which demonstrate that blood viscosity is not simply an unimportant consequence of transporting oxygen using hemoglobin but a variable which is under homeostatic control.

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