DIPLOMARBEIT

Rheological characterization of camel blood

zur Erlangung des akademischen Grades

Doktorin der gesamten Heilkunde

(Dr. med.univ.)

an der

Medizinischen Universität Wien

ausgeführt an

der Abteilung Dezentrale Biomedizinische Einrichtung

des Departments Biomedizinische Forschung

unter der Anleitung von

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Ort, Datum Unterschrift

Acknowledgements

I would like to thank my supervisor, ao. Univ. Prof. Dr. med. Vet. Ursula Windberger, for her guidance, her valuable and constructive suggestions, as well as her prompt and helpful responses to my queries and questions. Furthermore, I am very grateful to the camel farms of Würflach and Schloss Hof, without their collaboration this study would not have been possible.

I would also like to acknowledge the encouragement and support of Anna Stinglmeier, Aylin Bilir and Mario Mamerler, while I was writing the diploma thesis.

Finally, I wish to thank my family and friends for their support throughout my studies at the Medical University of Vienna.

Zusammenfassung

Hintergründe: 2017 wurde die Blutviskosität von zehn Dromedaren gemessen und die Ergebnisse waren beeindruckend. Die Blutviskosität zeigte niedrige Werte, weniger Fluktuationen der Viskosität bei unterschiedlichen Temperaturen, sowie eine reduzierte Scherverdünnung im Vergleich zu anderen Säugetieren. Damit verhält sich das Blut der Dromedare beinahe wie eine newtonsche Flüssigkeit. (1) Diese Studie befasste sich mit der zweiten Gruppe der Altweltkamele, den Baktrischen Kamelen, und sollte Aussagen, ob die Altweltkamele identische hämorheologische Eigenschaften aufweisen.

Methoden: Die Blutviskosität von 9 Baktrischen Kamelen wurde mit einem Rheometer bei unterschiedlichen Scherraten, Temperaturen und Hämatokriten gemessen. Diese Daten wurden danach mit den Daten von 10 Dromedaren und 5 Menschen verglichen. Anhand des Mann-Whitney *U* tests, linearer Regression und einem *t*-test für unabhängige Stichproben wurde der Unterschied der Blutviskositätswerte, die Temperaturabhängigkeit der Blutviskosität, sowie das scherverdünnende Verhalten zwischen Baktrischen Kamelen und Dromedaren verglichen.

Ergebnisse: Das Blut der Baktrischen Kamele und der Dromedare zeigte keinen signifikanten Unterschied der Blutviskositätswerte und die Temperaturabhängigkeit der Blutviskosität war in beiden Tieren ähnlich. Die Scherverdünnung des Baktrischen Blutes war jedoch höher und abhängig von der Temperatur. Wenn die Temperatur erhöht wurde, verringerte sich die Scherverdünnung im Blut der Baktrischen Kamelen, während die Scherverdünnung der Dromedare konstant blieb.

Schlussfolgerung: Es gibt subtile Unterschiede zwischen dem Blut der Baktrischen Kamelen und der Dromedare und deshalb kann man schlussfolgern, dass Altweltkamele nicht identische hämorheologische Eigenschaften besitzen.

Abstract

Background: In the year 2017 the blood viscosity of ten dromedary camels was studied and the results were extraordinary. The dromedary camel blood showed low viscosity values, fewer fluctuations in viscosity depending on the temperature as well as reduced shear thinning compared to other mammals, which makes the blood behave near-Newtonian (1). This study focused on the second group of Old World camels, which are the Bactrian camels and was designed to determine if both Old World camels have identical hemorheological properties.

Methods: The viscosity of 9 Bactrian camel's blood was measured with a rheometer at different shear rates, temperatures and hematocrits. The obtained data was compared to the data of 10 dromedary camels and 5 humans. By using the Mann-Whitney *U* test, linear regression and the independent sample *t*-test the difference of viscosity values, temperature dependency of blood viscosity, and shear thinning behaviour was compared between Bactrian and dromedary camels.

Results: Bactrian and dromedary camel blood show no significant differences in viscosity values and the temperature dependency of the blood viscosity is similar in both animals. However, shear thinning is higher in Bactrian camels compared to dromedary camels and is dependent on the temperature. When the temperature is raised, shear thinning decreases in Bactrian camels, while staying constant in dromedary camels.

Conclusions: There are subtle differences between Bactrian and dromedary camel blood and thus the conclusion can be drawn, that Old World camels do not have identical hemorheological properties.

1. Background

1.1. Hemorheology

1.1.1. Basic Terminology

Rheology, hemorheology

The word rheology was assigned to the field of studying the deformation and flow of matter in the 1920's (2) and originates from the Greek word "rhei" meaning "to flow". It is a branch of physics and is relevant to various fields including material science, engineering, geophysics, pharmaceutics, as well as physiology. (3) Within physiological studies concerning rheology the most important subspecialty is hemorheology, which is the study of blood flow within a vessel; a central focus is how the behaviour of blood is impacted when physiological external forces are present. (4)

Viscosity

The flow of fluids (gases and liquids) is a result of external forces (e.g. shear) and intrinsic fluid properties, also affected by the geometry in which the fluid flows. The intrinsic properties are generally described by the viscosity in the unit of Pa * s, which is a result of internal friction of shifting layers when a material is forced to flow. When viscosity increases, the flow is reduced at a given driving pressure; when viscosity decreases, it flows more easily. Viscosity is generally high if the bonds between the elements of the fluid are strong, and weak if the elements can easily be displaced relative to each other. An example would be heating, which would cause the interactions to decrease and with it the viscosity as well. (5-7)

Shear rate and shear stress

Shear (strain) rate ($\dot{y}$), also called rate of deformation or shear gradient measured in s^{-1}, is the ratio of the infinitesimal velocity (v) difference between two adjacent flow layers and the infinitesimal height (x) of a flow layer.

$$\dot{y} = dv/dx$$

Shear stress (τ) is the force (F) exercised on the area (A) of a fluid layer, whereby the direction vector is not perpendicular, but parallel to this layer. It is measured in Pa.

$$\tau = F/A$$

The resulting deformation of the material can be imagined by changing the rectangular shape of the layer into a parallelogram (see Figure 1).

Shear rate and shear stress influence viscosity if coupling between the fluid elements occurs. The relation between viscosity, shear rate and shear stress is described in this formula:

$$\tau = \eta\dot{\gamma}$$

Shear strain

The shear strain (also called shear deformation) describes the parallel shift (s) of all layers of a material composing a certain height (h) perpendicular to their original length and is used in the description of solid matter (8). Figure 1 shows that a layer close to the stationary plate shifts less than a layer on the moving plate. The difference between shear rate and shear strain lies in the effect of time. Shear rate is the time derivative of shear strain or in other words, the rate of deformation over time.

$$\gamma = s/h$$

(γ is the shear strain and since s and h are both measured in m, γ is dimensionless)

***Figure 1*: The rectangle made up of solid lines depicts an object in its original state; the dotted lines depict it after deformation has taken place. (Source: own construction)**

Newtonian liquids

In a Newtonian liquid the shear rate is directly proportional to the shear stress (see Figure 2); therefore viscosity is constant. The slope of the linear τ-ẏ-relationship reflects the viscosity value. In Newtonian liquids there is no interaction between the components. An example of this behaviour is shown by water.

Non-Newtonian liquids

Most liquids are non-Newtonian, and they can differ in two ways from the behaviour of Newtonian fluids. The shear stress in the liquid can become progressively higher or lower when the shear rate increases (see Figure 2). If the shear stress increases as the applied shear rate becomes high, the behaviour is called shear thickening and an example of it is a mixture of starch and water: When someone slowly places their hand within the mixture it behaves like a liquid and the hand can submerge; however if the person wants to hit the mixture it will stiffen and behaves like a solid object which allows the person to pound the surface. In

contrast, if the shear stress decreases as the applied shear stress becomes high, the behaviour is called shear thinning and human blood offers an example of this behaviour; e.g. in arterioles the shear rate (>500 s^{-1}) and stress (6-8 Pa) are generally increased compared to other blood vessels, which results in a reduced viscosity. (5-7)

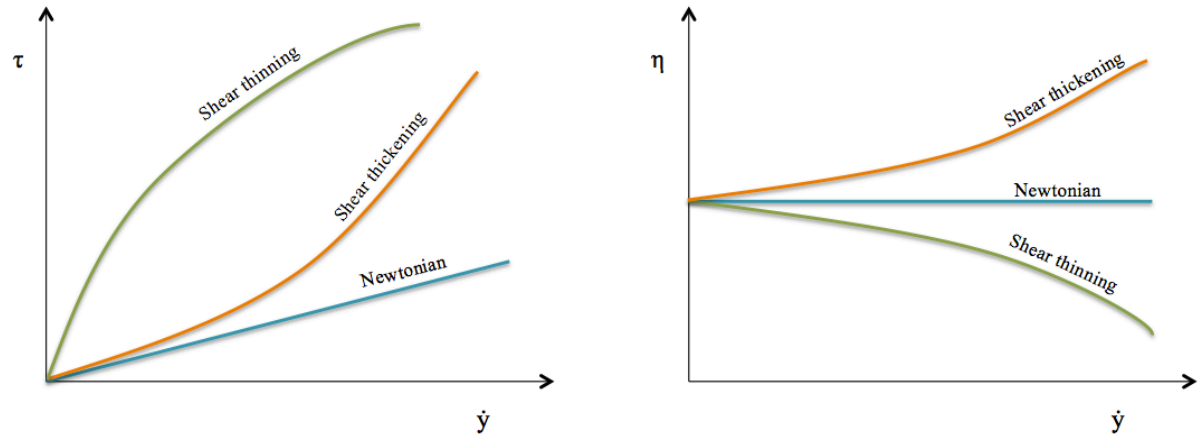

***Figure 2*: On the left the relationship between shear rate and shear stress, on the right the viscosity of Newtonian, shear thinning and shear thickening fluids depending on the shear rate is given. (Source: own construction)**

1.1.2. History of Hemorheology

The study of hemorheology was properly set in motion approximately in the past fifty years, however the interest in studying blood goes back to ancient times, when the Greeks noticed blood separating in different layers when being left untouched in a vertical tube. (9) They identified four different layers, which were made up of plasma being on top, followed by a coat of leucocytes, platelets and fibrin and below this were the packed red cells. The fourth layer was a black coat made up of red blood cells (RBCs), which were not oxygenated. (10) The Greeks did not identify the components of the different layers, however they noticed the separation of the layers varying depending on certain diseases and used this as diagnostic tool. In the Middle Ages blood continued to be a subject of fascination and blood letting was introduced as a treatment for different ailments. The efficacy was low and often patients were further weakened – sometimes to the extent of the patient dying. (9) This was obviously no ideal treatment, interestingly enough the concept of blood letting is closely related to that of hemodilution, which was developed in the twentieth century to reduce blood viscosity and thus assist the blood flow. (11)

In the early seventeenth century a major breakthrough took place through the discovery of blood circulation by William Harvey. This meant that blood flow was a vital part of the human body being able to function. William Harvey had presumed this by studying the valves of the veins and the heart (12) and decades later Anthoni van Leeuwenhoek confirmed this

discovery after being able to see microcirculation through the microscope and finding the link between arteries and veins. Van Leeuwenhoek was also the first person to correctly describe RBCs and was further able to observe their aggregation; he took notice of how it was increased when inflammation was present. (9)

About a century later, in the year 1770, William Hewson found white blood cells and was able to make the connection between lymph glands and leucocytes. (13)

During the first half of the nineteenth century physicians took an interest in the regulation of blood flow. One of them was Jean Leonard Marie Poiseuille who assumed this was caused by the flow properties of blood. He observed the flow in glass tubes, but due to the difficulty when working with blood, he started observing simple fluids such as water and alcohol. Retrospectively we know that this is caused by blood being a non-Newtonian fluid, this however was not known at that time. 1840 he published his data and Hagenbach summarized them in the following formula called the Hagen-Poiseuille law: (14)

$$\mathbf{F/t = (\pi p r^4)/(8\eta l)}$$

(F/t = fluid flow rate, p = pressure across the tube, r = radius of the tube, l = length of the tube, η = viscosity of the fluid)

This law describes the factors determining the flow of Newtonian fluids through cylindrical tubes. Although not appropriate, it is still used to describe non-Newtonian fluids. This can be considered the beginning of hemorheological studies.

In the beginning of the twentieth century the interest in RBC aggregation was renewed and Robin Fåhraeus developed the simple and cheap Erythrocyte Sedimentation Rate (ESR) Test, which is still routinely done to this day. He further started studying blood flow in microvessels and discovered, that red cells flowed as a train of aggregated RBCs in the centre of the vessel, whereas the marginal layer was cell-depleted. (9) He continued his studies with Johan Lindqvist and together they presumed that viscosity decreases with a decreasing vessel diameter, however when the diameter is as big or even smaller than the RBCs, the viscosity rapidly increases due to the lack of the cell-depleted layer and since the RBCs are maximally deformed. Regardless of this fact the RBCs are forced to squeeze through the narrow channels by the hydrodynamic pressure, which enhances viscosity. (15) This effect is called the Fåhraeus-Lindqvist Effect and the shear-thinning property of blood became apparent. (16)

During this time also Whittaker and Winton made a significant observation as they performed a forward thinking study on an isolated hind leg of a dog and perfused it with blood of varying hematocrits (HCT) and various driving pressures and showed a logarithmic

relationship between viscosity and HCT. (17) Later on, in the second half of the twentieth century, more in-vivo studies followed. Moreover also viscometers appeared which could measure viscosity in a standardized manner. This encouraged many physicians and engineers to study the viscometric properties of blood and started the initiation of journals, societies and congresses dedicated solely to the topic of hemorheology. The new tools stimulated many findings within the medical field; (9) following topics have been evaluated: mechanical properties of RBCs motivated by the discovery of blood viscosity being affected by stiffened cells (18), mechanics of white blood cells due to micropore flow being affected by leucocytes (19), adhesion of white and RBCs to the wall of blood vessels linked to pathological causes, such as diabetes, arteriosclerosis and in general inflammatory diseases, and equally pathological results, such as a thrombosis causing a local occlusion or embolism, being possible (20, 21), hemodilution as a treatment to increase blood flow (22), differences of hemorheological properties of neonatal blood compared to adult blood (23-25), the viscoelastic properties in athletes (26-30), effects of gravity of the viscosity (31) and many more. In the past decades species-specific differences have been investigated as well, like hemorheological compositions and properties, viscometric studies of whole blood or studies on single cell stiffness on: different types of primates, cats, dogs, rabbits, hamsters, guinea pig, cows, chicken, pigs, sheep, goats, geese, ducks, turkeys, horses, donkeys, rats, mice, frogs, toads, turtles, llamas, zebras, antelopes, crocodiles, Antarctic birds, penguins, icefish, seals, dolphins, whales, elefants, annelids, arthropods, Moschus javanicus and different types of aquatic salamanders. (32)

1.1.3. Methods of measuring viscosity

Until the 1960s the measurements within the field of hemorheology were limited to plasma and serum, which were considered to be Newtonian liquids, due to the fact that the first viscometers did not work at defined shear rates. However since then new methods have been generated to measure viscosity at different shear rates, also including the low shear rates. Viscometers use either a stationary object with the fluid passing it, or a stationary fluid with an object moving through it. Due to different parameters measured (often geometry and density), one can calculate the viscosity. (9)

1.1.3.1. Viscometers

More commonly used methods are listed below.

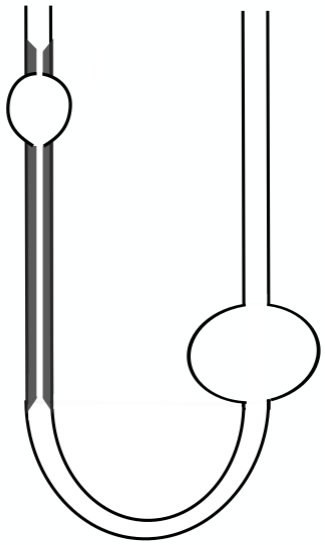

***Figure 3*: Schematic diagram of a capillary viscometer. (Source: Joanna Kośmider, 2014 (33))**

Capillary viscometers

The first types of viscometers used measured the rate of flow through a tube of specific dimensions. A common version of the capillary viscometer is a U-shaped glass tube, which is placed vertically in a temperature-controlled bath. The tube contains two bulbs and a narrow section connects these. There are two marks around the first bulb and the time needed to pass between these two marks can be used to calculate the viscosity. Shear stress occurs in the capillary tube, however it varies depending on the location within the tube; in the centre the shear stress is zero and it is highest at the wall. Furthermore the sample is exposed to varying shear rate. Due to this, this method of measuring is unsuitable for non-Newtonian fluids, however it has been frequently used to successfully measure the viscosity of plasma and serum. (9, 34)

Falling ball viscometers

These viscometers use a vertical tube filled with the test fluid. The time is measured for a ball (made out of glass or steel) to pass a certain distance within the tube. This viscometer is also unsuitable for the measurement of non-Newtonian fluids. (9)

Vibrational viscometers

An oscillating electromechanical resonator is immersed into the test fluid and either the electrical power needed to maintain the amplitude of oscillation within the sample, or the time until the oscillation in the sample has passed after switching off the resonator is measured. Since a high viscosity makes it more difficult to maintain the oscillation amplitude, more power is needed, and the oscillation also stops earlier when the resonator is abruptly turned off. (35) Since the commonly used vibrational viscometers do not apply a defined shearing, they are usually inappropriate for the measurement of whole blood, however in the past decade more sophisticated vibrational viscometers are being developed. (36)

Rotational viscometers

The test fluid is filled into the gap between two metallic surfaces, with one surface being static while the other one rotates at different speeds to generate the shear rates. The test

principle consists of measuring the resistance of the fluid against rotation by recording the shear stress transmitted by the sample. In most systems the shear stress is measured by the torque on the static surface, however other systems use the rotating surface for both applying shear rates and measuring the developed shear stresses as well. Different geometrics are available.

- *Concentric cylinder*

  This system uses a fixed and a rotating cylinder placed within each other. The inner cylinder is called the bob and the outer one is called the cup. In the Couette type viscometer the cup rotates and in of the Searle type viscometer the bob rotates. The advantages of these devices lie in a high surface area with little sample evaporation, making the measurements highly sensitive. However the shear rate is not linearly distributed in the gap width, although lowering the gap can minimize differences. (9, 37)

- *Cone and plate*

  A fluid is placed on a horizontal plate and then a cone is immersed into it. The angle between the cone and plate is usually very shallow, about 1 degree. These geometries produce a uniform shear rate in the whole gap. Although the velocity increases toward the periphery, the distance between both surfaces increases as well, which allows a constant velocity gradient and thus a constant shear rate. The gap between the cone and the plate cannot be changed. (9, 38, 39)

- *Parallel plate*

  This viscometer consists of two parallel discs. The gap between the discs is usually 1 mm or less, but can be increased, which makes the parallel plate viscometer very practical for many industrial purposes, because it allows the study of substances such as concrete that need more space. A disadvantage of the geometry is that the shear rate is not uniform. (40-42)

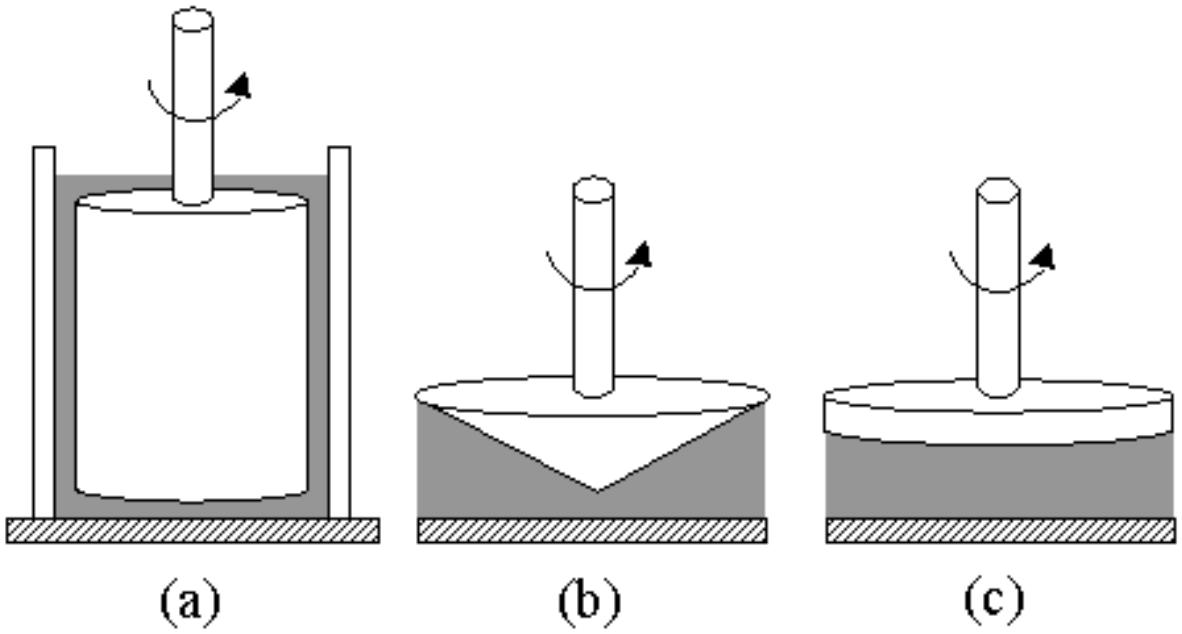

***Figure 4*: Schematic diagram of rotational viscometers: (a) concentric cylinder, (b) cone and plate, (c) parallel plate (Source: National Institute of Standards and Technology, n.d. (43))**

Oscillatory-flow viscometers

In the past decades oscillatory flow has been implemented to rotational and tube viscometers. These viscometers are called rheometers and allow conclusions about the elastic properties of a viscoelastic solid material as well. (9, 44) Using the parallel plate model as an example of how this works, the upper plate rotates and a push rod is attached to it. The rod causes the plate to move back and forth parallel to the lower plate and the sample in-between oscillates. As long as the rotational speed is constant, the oscillating frequency will be constant as well and variations of the shear stress and strain take place, which are both measured. In a diagram these variations result in sine curves over time with the strain amplitude γ_A and the shear-stress amplitude τ_A. These amplitudes are used to calculate the "complex shear modulus", which describes the entire viscoelastic behaviour in a sample:

$$\mathbf{G^* = \tau_A/\gamma_A}$$

(G* is the complex shear modulus in Pa, τ_A is the shear-stress amplitude in Pa and γ_A is the dimensionless strain amplitude)

It is even possible to determine the energy stored and lost when deformation takes place. To calculate this, a vector diagram is created using G* and the lag time in-between the shear strain and stress. The lag-time equals the phase shift δ, which is an angle always between 0° and 90° (0° to 45° equal a solid or gel-like sample, while 45° to 90° describe a fluid). (see figure 5) This angle is placed below a vector of the length of the G* value. (see figure 6) The

part of the G* value alongside the x-axis corresponds to the stored deformation energy called storage modulus G', which causes the structure to return into its original shape as soon as the force generating the deformation is released. The value alongside the y-axis depicts the lost (dissipated) deformation energy called loss modulus G''. The strength of bonds between individual molecules in the sample tested determines the ratio between G' and G''; solids have stronger bonds and thus the storage modulus is greater than the loss modulus, while the weaker bonds within fluids cause the loss modulus to be greater. (8)

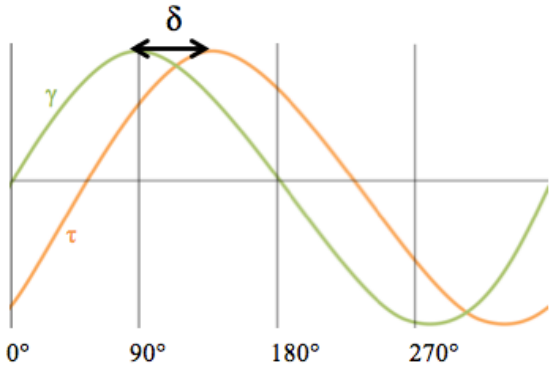

***Figure 5*: The time lag between the shear strain γ and shear stress τ amounts to the phase shift δ (Source: own construction)**

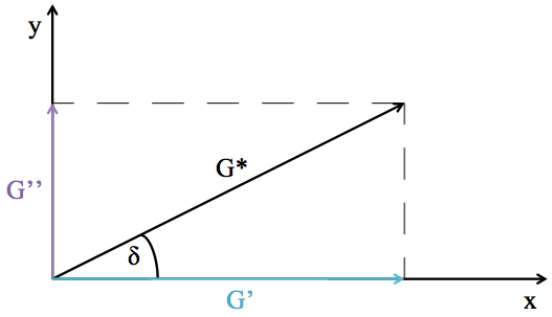

***Figure 6*: Calculation of the storage modulus G' and loss modulus G'' using the complex shear modulus G* as a vector and the phase shift δ (Source: own construction)**

1.1.3.2. Limitations of in vitro measurements

When measuring the viscosity of blood in vitro there are certain limitations; the vascular geometry causing the distribution of blood cells in a vessel cross-section and the pulsation within blood vessels are absent, likewise is the hydrated endothelium replaced by hard metal. Another limiting factor is that when blood comes into contact with air, plasma proteins form a film at the blood air interface. This film is semi rigid and produces an additional torque when measuring at low shear rates causing false results. (9) (45) However this can be overcome by inserting a "guard" ring within the rotational viscometer, which separates the film from the torque-sensing component. (9)

One should also keep in mind the aggregation of RBCs or their general tendency to migrate to fluid layers of lower shear. RBC aggregation usually does not take place at high shear rates, however, when measuring at low shear rates it can quickly lead to syneresis. Syneresis is the effect of particles in a fluid being drawn toward each other and away from the walls of the viscometer and results in progressive phase separation along with the test duration. (46) Syneresis is accelerated when RBC aggregates are present, but can also develop at high shear flow due to the elasticity of RBC membranes. In all circumstances, one should make sure that

the blood sample is mixed properly prior to measuring (45) and protocols should be present to detect the presence of syneresis.

1.1.4. Human blood

1.1.4.1. Composition and its influence on hemorheological properties

Blood is a vital medium with many important functions, such as transporting oxygen, nutrients and hormones to all tissues of the body and removing waste from them. Furthermore it helps to regulate the temperature and pH within the body and since it contains platelets, clotting factors and white blood cells, it is important for closing wounds and fighting off infections. (47)

To work properly, blood needs to navigate our complex vascular network, which varies in diameter from 3 cm to 5 µm and it has to be pumped at a certain rate against the peripheral resistance to upkeep its different tasks. The rate is driven by the pressure generated by the heart, the resistance of blood vessels and the flow properties of blood itself; the latter heavily depends on the composition of blood. (9)

Plasma

50-63% of human blood is made up of plasma. (47) It has long been considered to be a Newtonian fluid with a low viscosity ranging from 1,1 to 1,3 mPa*s at 37°C (48), until its viscoelasticity was found in extensional flow (49). Plasma contains about 90% water, with 10% being made up of ions, metabolites (e.g. glucose) and proteins.

Ions are the smallest solutes of plasma – their molecular weight is equivalent to a few tens of Daltons and make up 1% of the plasma. The most important ions pertaining to hemorheology are sodium (Na^+) and hydrogencarbonate (HCO_3^-). Na^+ is the most dominant ion within plasma with a normal concentration of 135-145 mmol/L. (50) Due to this, it has a huge impact on the osmotic property of blood; if the concentration of Na^+ rises or falls, RBCs will be affected by either shrinking or swelling. This changes the mechanical properties of RBCs and thus the blood viscosity. (51) HCO_3^- has a normal range from 24-30 mmol/L and its main function is to ensure a constant pH within 7,35-7,45. (50) Keeping up this range is vital for normal body functions and changing the pH will affect RBC shape and deformability as well, again influencing the viscosity. (52)

The metabolic molecules, which weigh a few hundred Daltons, make up 2% of the plasma. There impact on the blood viscosity is limited. (9)

Proteins make up 7% of plasma with the different proteins weighing millions of Daltons. They are necessary to carry vital materials, to fight off infections and for haemostasis. (50) Since they are large and often have asymmetrical shapes, they impact the plasma viscosity significantly – at 37°C normal human plasma viscosity is 1,25 ± 0,1 mPa*s and in comparison the viscosity of water is 0,69 mPa*s; this difference is mainly due to the proteins. (53) Furthermore the proteins, mainly fibrinogen with a normal range of 3,5 ± 0,4 g/L (54), cause RBCs to loosely stick together (see "cells" below for more information). This significantly impacts the blood viscosity. (9)

Cells

36 to 50% of human blood is made up of RBCs, which makes them the predominant blood cell. They are shaped as biconcave discs with a diameter of about 8,5 µm and a thickness of about 2,4 µm. Their mean corpuscular volume (MCV) normally ranges from 83 to 101 fL. However, new RBCs can have a volume up to 120 fL, while the older ones (120 days old) can have a lower volume of about 60 fL.

RBCs determine whole blood viscosity not only due to their quantity, but also due to their behaviour in flow. A very slowly flowing RBC rotates around its axis with the angular velocity of the suspension medium (the cell tumbles) even if it is flexible. When the flow increases, more coordinated motions are feasible for the RBC, which allow its alignment in the flow field. The threshold at which a RBC starts to switch from tumbling into rolling and further into tank-treading depends on the deformability of the membrane and the ability of the bilayer and the cytoplasm to dissipate the viscous forces that are applied to the cell by the surrounding plasma flow. (1). Since human RBCs deform and elongate under high shear forces, the viscosity decreases noticeably (see 1.1.4.2 Red blood cell deformability for more information on the deformation of RBCs). On the other hand, if the shear rate is low, fibrinogen causes RBCs to loosely stick together and make them look like a pile of coins. This is called the rouleaux formation and when it takes place, the viscosity rises. (9)

The RBCs volume fraction also impacts the viscosity – the higher the HCT, the higher the viscosity and vice versa. (9, 55)

In comparison, the remainder of the cellular components, which are white blood cells and platelets, make up only 1% of the total blood volume. Inactive platelets are small discs with a diameter of 2-3 µm and rather represent tracer elements. However, white blood cells are large and round cells, the most common ones ranging from 8 to 15 µm in diameter (47), and play

an important part in microcirculation not only due to their size but also due to their potential adhesivity to the vessel wall. Small white blood cells, such as T- and B-cells, have a volume of 120 fL, which is 20% higher than the volume of RBCs, but monocytes have a volume of 230 fL. Since the smallest blood vessels have diameters of 5 µm, these large cells impact the overall resistance of microcirculation. Despite this, white blood cells do not play an important role in the blood flow in large vessels. (9)

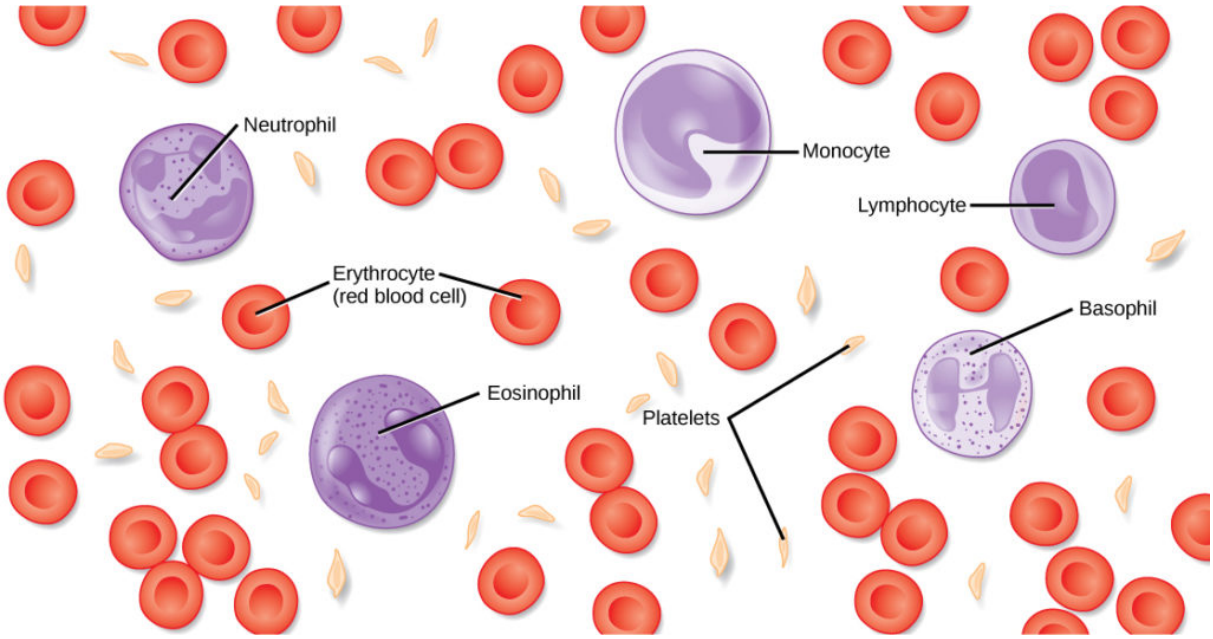

***Figure 7*: The cellular components (Source: Lumen learning, n.d. (56))**

1.1.4.2. Red blood cell deformability

The deformability of RBCs has been observed and measured directly by using rheoscopes, ektacytometry and optical tweezers, as well as indirectly by measuring the pressure or time needed for RBCs passing pores of filters or capillaries smaller in diameter than the cells themselves. It has been shown, that the deformation increases with shear stress. (57, 58) The association between deformability and whole blood viscosity is established through the progressive decrease in viscosity with increasing shear rates when RBC deformation is possible. When this deformation is either reduced or cannot take place anymore the viscosity rises. In suspensions containing rigidified RBCs the viscosity was increased at high shear rates, and when the ability to deform was completely abolished (by fixating the RBCs in aldehyde) even shear thickening took place. (59)

The deformability occurs through the specific structure of the RBC. The membrane is made up of a lipid bilayer with a thickness of 40 to 50 nm (60), which is mainly composed of phospholipids and cholesterol. The lipid membrane behaves as an incompressible fluid, and affects RBC deformability by a certain bending resistance. Its main task is to dissipate viscous

forces during blood flow. But within the lipid bilayer, several skeletal proteins are located to uphold the structure of the membrane and to prevent it from collapsing. The most important protein complexes to anchor the spectrin cytoskeleton are the ankyrin and the 4.1 complexes, which form a hexagonal like lattice with the underlying spectrin molecules. The membrane cytoskeleton and its anchor to the bilayer provide resistance against deformation and therefore provide certain stiffness to the cell. But at the same time the membrane proteins maintain a constant surface area of the membrane while deformation takes place and stabilize the bilayer in-between the protein clusters. (61)

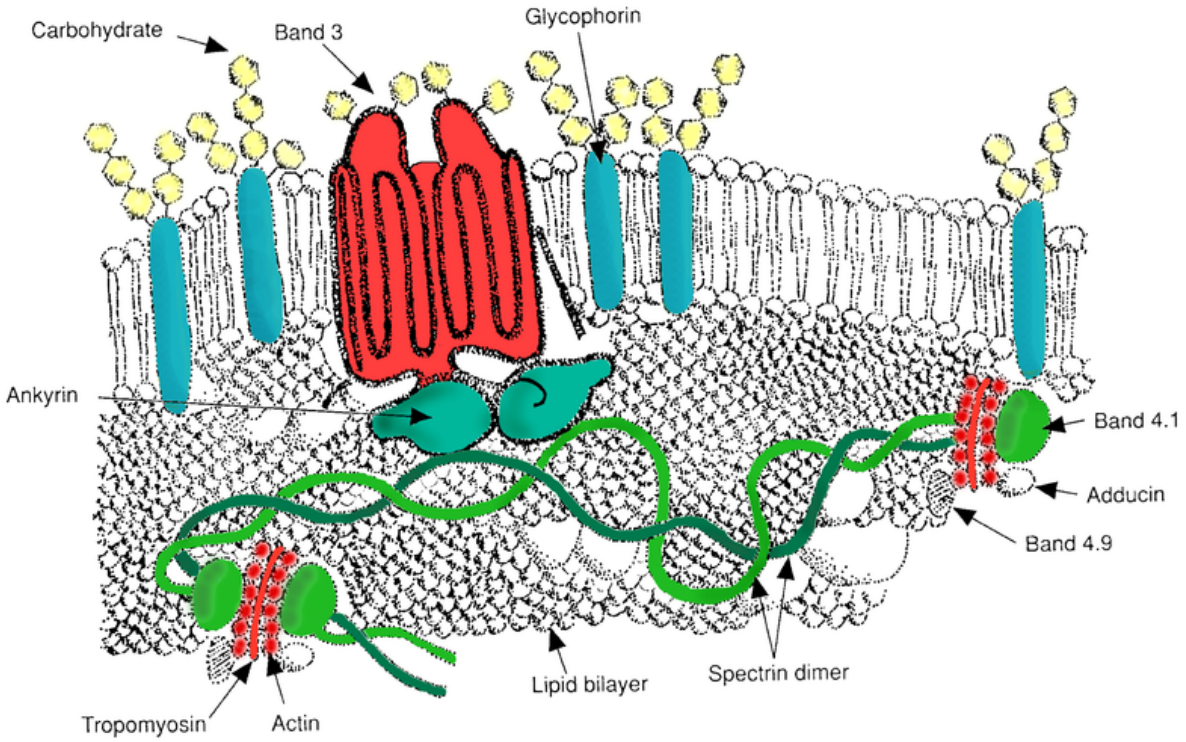

***Figure 8*: The structure of red blood cell membrane. (Source: Ernst Hempelmann and Tim Vickers, 2009 (62))**

The cytosol is a Newtonian solution containing salts (Na^+, Cl^-, K^+, HCO_3^-) and different proteins with haemoglobin being the most abundant. The viscosity of the cytosol solution is 6,5 mPa*s in a physiological environment, meaning at a temperature of 37°C and with a concentration of haemoglobin at 33 g/dL. (63, 64) When comparing the surface of the RBC to the volume it contains, the cell is deflated. (61) The surface of an average human RBC is 135 μm^2 and a RBC contains a volume of about 94 μm^3 (65, 66), however 100 μm^2 would suffice to cover this volume. The excess surface allows for the deformation of the RBC without changing the volume or the surface area (= isochoric deformation). (67)

The behaviour of RBCs in blood flow (and therefore blood viscosity) is not only influenced by cell deformability but also by the viscosity contrast, which is the ratio of cytosol viscosity and plasma viscosity. In humans the viscosity contrast is approximately five in physiological

conditions. The lower this contrast is, the better the RBCs will be embedded in the surrounding plasma and will move more fluently through it. When the contrast is raised, higher shear rates are needed for RBCs to become deformed, and at very high viscosity contrast RBCs loose the ability to deform at all. (68) RBCs that do not deform will not align in the flow streamlines, which raise the viscosity at high shear rates. RBCs that tumble extensively will not be able to form rouleaux, which lowers viscosity at low shear rates. Both situations thus decrease the shear thinning behaviour. (69-71) An increase of the viscosity contrast can pathologically occur in conditions where MCHC is increased, for instance during extreme dehydration or hereditary spherocytosis.

1.1.4.3. Blood flow in small vessels

In vessels with diameters of less than 300 µm the average HCT value decreases with decreasing tube diameter. This observation was called the Fåhraeus effect and it is caused by the RBC flow behaviour. Due to their membrane elasticity, RBCs flow toward the central region of a vessel when flowing downstream (they migrate to regions of lower shear where they can better relax their strained form); thus the RBCs accumulate in the centre of vessels. When a vessel gives off smaller branches, the portion of blood flowing alongside the vessels wall, which now contains fewer RBCs, will flow into these branches and the daughter vessel will contain less RBCs. Blood viscosity therefore decreases with the vessels diameter, since viscosity is influenced by the HCT. This is called the Fåhraeus-Lindqvist effect. (9)

However, a particular diameter cannot be ascribed a specific HCT even within one person. Another effect that influences RBC distribution in microvascular networks is called Zweifach-Fung effect. This effect describes the change of local perfusion due to the dynamic change of vascular resistance. Blood cells generally distribute into regions of lower resistance. In asymmetric bifurcations, RBCs tend to flow into the daughter branch with the lower resistance. This generates a high viscosity in this daughter vessel, whereas the other daughter vessel becomes deprived from RBCs, sometimes even resulting in a RBC fraction reaching zero. As the resistance becomes lower with time, the picture turns, and RBC flow into the deprived daughter vessel increases, whereas the former “hyperperfused” one becomes deprived for a short time period (72-74)

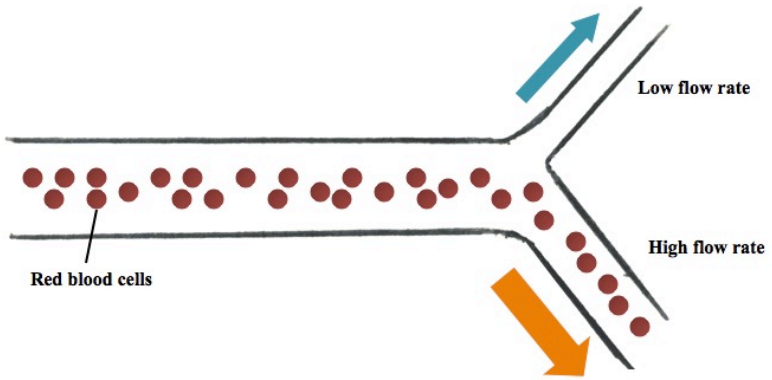

***Figure 9*: The Zweifach-Fung effect in an asymmetric bifurcation. The daughter vessel with a higher flow rate has a lower resistance, which is why the RBCs flow into this vessel. (Source: own construction)**

White blood cells and platelets flow differently compared to RBCs. Platelets always flow alongside the vessels wall because they are small and enrich in the so-called cell-free plasma layer. They are also pushed there by the flowing RBC column. (75) White blood cells behave more complex; their radial distribution is affected by the blood flow rate. At low flow rates the RBC column pushes the white blood cells toward the vessels wall as well. At high flow rates they follow the same principles as RBCs due to their size and flow in the centre of vessels. (76, 77)

1.1.4.4. Hyperviscosity syndrome

Some diseases or circumstances cause the blood viscosity to increase and this can be very problematic due to the possible occurrence of the sludge phenomenon. It is a disturbance in microcirculation when RBCs aggregate temporarily – organs then suffer because of hypoperfusion and long lasting damages can occur. (78)

The most common disease causing hyperviscosity is the Waldenstrom macroglobulinemia, followed by the multiple myeloma. These diseases affect the production of plasma proteins; the amount in which some proteins are produced is increased, as well as them being enlarged (e.g. Waldenstrom macroglobulinemia mainly affects immunoglobulin M). (79) Pathological changes in RBCs can also be a cause of an increased viscosity. Anaemia itself does not cause hemorheological problems, however, if the deformability is disturbed (e.g. thalassemia and sickle cell anaemia) the microcirculation will be affected negatively. (80) For example sickle cell anaemia causes RBCs to become more rigid when the oxygen supply decreases (i.e. in microcirculation). However, they change back to their normal state when they are resupplied with oxygen. This leads to low resistance in flow in large vessels and increased resistance in microcirculation and the constant change of rigidity irreversibly damages the RBCs after some time. This can possibly lead to stasis long term. (81, 82) Aside from causes related to

the RBCs and the plasma proteins, even a massive increase in leucocytes can lead to hyperviscosity; this can happen in some cases of leukaemia. (78, 83)

Typical symptoms of the hyperviscosity syndrome include mucosal bleeding (e.g. epistaxis) due to platelet aggregation being prolonged when the amount of circulating proteins is increased, visual disturbances due to retinopathy after thrombosis and microhemorrhages, and a variety of neurological symptoms such as headaches, dizziness, seizures, stroke syndromes and even coma. (78)

1.2. Comparative Hemorheology

Hemorheological properties vary widely among species, and to further the understanding of the structure-function relationships between RBCs and physiological mechanisms several comparative studies have been undertaken. Many differences concerning blood rheology have been observed, some species-specific properties would even be pathological in humans. Often these differences reflect different ways of living or an adaption of the animal to a specific environment. The most investigated group of animals are mammals and this section will focus on varying observations within this vertebrate class.

Mammals are the only animals that do not contain a nucleus within the RBCs, and in most species RBCs are biconcave discs. This allows the shear forces to induce greater modifications of the RBC shape. Most mammals have a HCT of 30-50%, which is similar to the human reference value, however, RBC aggregation and deformability vary strongly in-between different species and can be substantially different to human. (9)

Shape and size of RBCs, blood cell count, and blood plasma composition have a huge impact on blood flow. Goats have a very small RBC volume with a mean of 18 fL, on the other side of the spectrum giant anteaters have a RBC volume of 160 fL, with other mammals laying in between. The size of the animal itself does not impact the RBC volume. (84) However there is an inverse correlation between the MCV and the RBC count. (85, 86) There are variations in the mean MCHC, e.g. seals have a high MCHC and this probably serves the purpose of storing more O_2 for long-term dives. On the downside this leads to a higher cytoplasmatic viscosity, which might affect the deformability of their RBCs. (87) Plasma viscosity varies depending on the plasma protein concentration (cattle have a high plasma viscosity of 1,72 mPa*s, rabbits have a low plasma viscosity of 1,30 mPa*s). However plasma viscosity does not correlate with the whole blood viscosity between species; e.g. horses have a high whole blood viscosity despite a low plasma viscosity and cattle, on the other hand, have a high plasma viscosity due to a large amount of fibrinogen, but the whole blood viscosity is low at

low shear rates. (88) Another observation concerns the influence of HCT and temperature on the whole blood viscosity – generally there is a correlation between these factors, however the extent of the impact can differ; e.g. the whole blood viscosity of bowhead whales, which live in a cold environment, is less influenced by temperatures when comparing them to other mammals living in less extreme temperature conditions. (89) Furthermore RBC aggregation has an impact on the extent of shear thinning; low rates of aggregation correlate with less shear thinning and vice versa. (88, 89) Aggregation is influenced by RBC deformability, membrane surface properties (90-92) and differences in plasma protein concentrations. (93, 94) Generally mammals can be split into three categories: hyperaggregation (horses, rhinoceros), medium aggregation (primates, pigs, elephants, rabbits) and "no" (very little) aggregation (camelids, cows, sheep, goats).

1.3. Camels

1.3.1. Taxonomy

***Figure 10*: The Bactrian camel is depicted on the top left (Source: own construction) and next to it the dromedary camel (Source: Adapted from: John O'Neill, 2007 (95)). Below and from left to right are photographs of a llama (Source: Adapted from: Johann Dréo, 2007 (96)), an alpaca (Source: Adapted from: Tony Hisgett, 2016 (97)), a vicuña (Source: Adapted from: David Torres Costales, 2011 (98)) and a guanaco (Source: Adapted from: "fainman", 2007 (99)).**

Camelidae is the only surviving family in the group of tylopods ("swollen foot"), which is an archaic group of animals dating back up to 46 million years ago. They belong to the order of artiodactyla ("even-toed ungulates"). Camelidae themselves are split into Old and New World camels. Llamas, alpacas, guanacos and vicuñas are New World camels and native to the South American Andes regions. The Old World camels are Bactrian camels (*camelus bactrianus*; also called two-humped camel) and wild camels (*camelus ferus*), which are native to Asia, as well as dromedaries (*camelus dromedarius*; also called one-humped camel), which are found in Arabia and North Africa. (100)

1.3.2. Temperature regulation and dehydration

Camels live in harsh climates. Bactrian camels are native to rocky deserts in Central and East Asia and endure temperatures from -20 °C to 40 °C, as well as a limited access to water. (101) They deal with extreme ambient temperature by their ability to adapt the body temperature to the ambient temperature (the body temperature can range from 34 °C to 42 °C) and by the possibility of selective brain cooling. (102, 103) They are equipped by anatomic features such as a thick fur on the back that protects from the sun, by long cilia that protect the eye from sand, and by pads, covered with thick protective soles on the feet that keep from sinking into loose sand and protect from hot desert sands. Camels also use more sophisticated methods to conserve water and energy. (101) For example when a dehydrated camel inhales, the air flow dries out the large nasal surface and creates a layer of dry mucous and cellular debris, which is hygroscopic, and takes up water from exhaled air. This cools the blood in surrounding vessels (102), and also saves water expenditure. Camels also rarely sweat, produce low volumes of concentrated urine and little saliva, and have a low metabolic rate, which helps them conserve water. (101, 104) These mechanisms help the camel to reduce their water expenditures 2 to 3 fold compared to other mammals (105-107). The main mechanism allowing camels to survive several weeks only by eating salty plants in the desert and without drinking water is by storing fat in their humps, which can be converted into water and energy needed. When they drink, however, they can take up notable volumes of up to 140 L within 13 minutes. (101) Studies are available showing the blood composition as well as the RBC morphology during dehydrated states. While the increase of the lipid and protein concentration indicates the loss of plasma water (108), the increase of total protein was much lower compared to other artiodactyla, not adapted to a desert environment. After three days of depriving of food and water the total protein increased by more than 20% in sheep and goat, while the increase of total protein in camels was much less with about 8%. (109)

After six days of depriving dromedary camels from food and water, the RBC count increased, indicative for blood "thickening". These changes were reversible within two hours after the camels drank water, however, the colour of the blood plasma remained yellowish. In goats, the RBCs were small and triangular shaped after three days of food and water deprivation and the authors suggest that they may gather even in such a way that they could block the blood flow in capillaries which would cause embolisms. It took twelve hours in goats after drinking to reverse these effects. (110) These differences of the impact of dehydration on RBCs show an impressive resilience of camel blood. Further studies show this behaviour of camel RBCs (111-113), signifying fewer changes in camel blood viscosity depending on the state of hydration compared to other animals. This is due to fewer fluctuations in blood composition and RBC shape in camels.

1.3.3. Hormonal patterns

In humans, several studies show the impact of sexual hormones on blood viscosity. (114-117) Oestrogens and progestogens increase the HCT and oestrogen additionally increases plasma fibrinogen concentration. Progesterone also impacts the viscosity by reducing RBC deformability. (118) It is very likely that sexual hormones will influence camel blood as well, and it is interesting to take a look at the reproductive physiology of camels. Camels become sexually mature when they are 4 to 5 years old and they are seasonal breeders (119-121). Their breeding season depends on the location and takes place during colder and rainier seasons to ensure that both the rutting season and the consequent births coincide with better water and food supplies. (122) For example the breeding season in India starts in November and comes to a close in February. (123) It takes place in completely different months from April to May in Somalia. (120) As well as being a seasonal breeder, the female camel is a polyoestrus animal, which means that ovulation takes place more than once during each breeding season. In dromedary camels the ovarian cycle is a 28-days cycle. Ova mature in 6 days, maintain their size for 13 days and then regress for 8 days. (124) The Bactrian camel seems to have an extended oestrus cycle of 30 to 40 days. (125) Ovulation occurs 30 to 48 hours after copulation and does not take place spontaneously. (126) Research in Israel showed that from the beginning of December until the beginning of April an increased level of oestradiol was measured in blood of dromedary camels. There were also peaks of progesterone activity as the oestradiol increased, which started off being 23 days apart. From the middle of January there were oestradiol peaks every 7th day, with following peaks of progesterone after 2 days. 24 to 48 hours after successful copulation with resulting

pregnancy, the luteinizing hormone (LH) appeared. LH declined after that, reaching a great peak after 2 weeks with high levels of progesterone. When progesterone was high, oestrogen levels were low, however, both hormones had alternating peaks every 4th day with low LH levels for the remaining pregnancy. (127) Gestation is reported to take place for 402 days in Bactrian camels, (126) however for the dromedary camel there are reports ranging from 365 to 395 days. (119, 121) When well fed, oestrus can occur one month post partum in the camel. (120, 121) Males are seasonal breeders as well and their rutting season corresponds with the one of the females. During this time an increased secretion of androgens can be found in the blood, as well as in the urine. (128)

When comparing the blood viscosity between camels the impact of age, gender and season on the sexual hormones must be kept in mind. If, like in human, sexual hormones influence blood viscosity, inter-individual differences of viscosity even within one herd might arise. E.g. sexually mature female camels may have a higher blood viscosity during the rutting season.

1.3.4. Hematology of camels

The research concerning hematological properties of camelid blood is on-going since decades, however most studies provide incomplete data, broad reference ranges, and methods are often not described in detail. Vap et al. summarized data from previous studies and provided reference intervals for camelids. Though the paper shows also data for Old and New World camelids, most data pertains to llamas (shown in table 1 below). Hematology was found comparable between Old and New World camels, though the reference intervals given are slightly lower in Old World camels. (129)

***Table 1*: Reference intervals for adult llamas by Vap et al., HCT = hematocrit, RBC = red blood cell count, Hb = haemoglobin, MCV = mean corpuscular volume, MCHC = mean corpuscular haemoglobin concentration, WBC = White blood cell count (Source: own construction based on Vap et al. (129))**

Parameter	Reference Intervals
HCT (%)	27 – 45
RBC (T/L)	10 – 17
Hb (g/dL)	11 – 19
MCV (fL)	21 – 31
MCHC (g/dL)	39 – 48
WBC ($x10^3/\mu L$)	7.5 – 22
Band neutrophils (G/L)	0 – 0.4
Segmented neutrophils (G/L)	4.6 – 16
Lymphocytes (G/L)	1 – 10
Monocytes (G/L)	< 1
Eosinophils (G/L)	0 – 5

Compared to human, camelids have a higher RBC count but a lower HCT due to a low MCV. The MCHC is enhanced, which gives rise to a high viscosity contrast. The amount of haemoglobin in a defined blood volume is comparable with the human reference value. (47) The morphology of the erythrocytes varies substantially from other mammals. The RBCs are not only smaller, but have an elliptical shape with major and minor diameters ranging from 8 µm to 3,8 µm (130). They are flat and lack the central pallor found in human RBCs; this is presumed to have resulted in falsely low RBC counts being given in the past (e.g. if particle counters are not set to the proper threshold settings needed for camel blood). In a few erythrocytes even rhomboid or hexagonal haemoglobin crystals have been found. No apparent reason for this finding has been reported and it is presumed not to be pathological. Reticulocyte counts are quite similar to human, however another interesting finding is that some camel bloods included low numbers of nucleated RBCs. (129) Furthermore, some RBCs contained a marginal band, which is an association of membrane-reinforcing bundles of microtubules that stabilize the RBC membrane. (32) The presence of a nucleus and intermediate fibers in camel RBCs is under debate, because adult mammalian red cells are typically deprived of such intracellular structures. However, it is still unclear how the elliptic form, the high membrane stiffness, and the high osmotic resistance of camelid RBCs can be achieved. A marginal band that stabilizes the membrane cytoskeleton would be one of possible explanations.

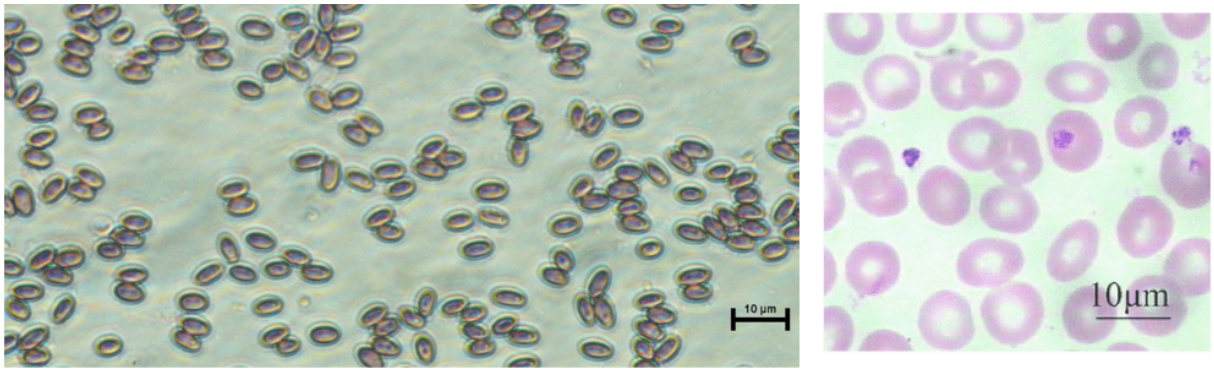

***Figure 11*: On the left: Bactrian camel red blood cells (Source: own construction), on the right: human red blood cells (Adapted from Li Y, Lu L, Li J, 2016 (131))**

Camelids also have a higher white blood cell count and their differential count varies greatly in comparison to human. The number of band neutrophils and lymphocytes is reduced, while segmented neutrophils and eosinophils are concentrated. The monocyte count resembles the one of human. (47) When comparing the white blood cells within camelids, the younger animals seem prone to having higher lymphocyte counts compared to the adults. Stress gives rise to neutrophilia, lymphopenia, as well as eosinopenia. Platelets are higher in number and smaller compared to many other mammalian species. (129)

1.3.5. Rheological properties of dromedary camel blood

The blood of well-hydrated dromedary camels that lived in their native environment in Dubai showed only marginal shear thinning, and the rheological behaviour was described as near-Newtonian. More than that even shear thickening was observed in RBC concentrates, since an augmented increase of viscosity is observed at higher shear rates when the HCT rises. (1)

When dromedary camel and human blood was compared at physiological HCT values, the dromedary camel blood generally had a lower viscosity compared to humans (133); whole blood viscosity was 3.74 mPa*s at 10 s^{-1} and 3.44 mPa*s at 1000 s^{-1} at 37 °C and 40% HCT. (1)

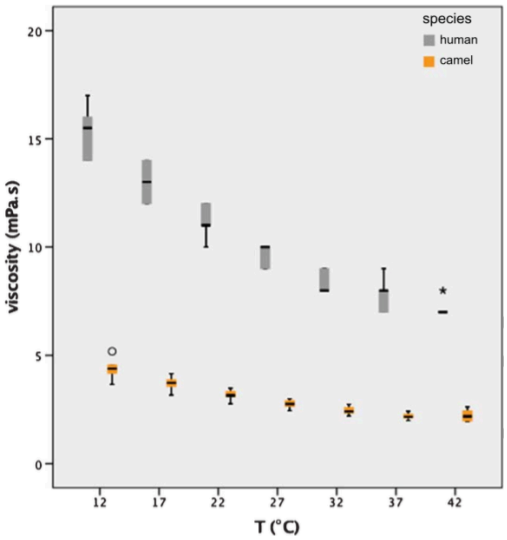

Figure 12: **Low shear rate (10 s-1) viscosity of whole blood (HCT 27%) of dromedary camels (n = 10) compared to human blood (n = 10) at 30% HCT. (Source: Windberger et al., 2018 (132))**

The low viscosity can be attributed to the lack of RBC aggregation and the low plasma viscosity (134). Another difference discovered was that the camel blood did not undergo extreme changes in viscosity when the temperature changed. Viscosity was about 2.18 mPa*s at 10 s^{-1} when the temperature was 42 °C and when lowering it to 12 °C it increased only to 4.39 mPa*s. At 1000 s^{-1} at 42 °C the viscosity was 2.00 mPa*s and at 12°C it was 3.98 mPa*s. Although a difference was observed it was noticeably smaller than in human; human blood has a viscosity of about 8.21 mPa*s at 10 s^{-1} when the temperature was 37 °C, and when lowering it to 12 °C it became 15.52 mPa*s. At 1000 s^{-1} at 37 °C it was 5.35 mPa*s, and at 12 °C it increased to 11.24 mPa*s. (133) This property of blood viscosity not being as much dependent on the temperature can be beneficial for dromedary camels because it could maintain homeostasis, since their body temperature can range between 34 °C and 42 °C during 24-hours.

Some rheological characteristics of dromedary camel blood can possibly be explained when taking a closer look at their RBC membrane. The membrane is also made up of a lipid bilayer, however the fatty acids have shorter and more unsaturated hydrocarbon chains, which result in a lower membrane cohesion and thus enables membrane fluidity. (135) Furthermore the protein-to-lipid ratio is shifted towards there being more proteins and this increases the connection to the cytoskeleton. (136-138) A factor that stiffens the membrane is that

dromedary camels have a much higher concentration of the membrane protein band 3 in comparison to humans. (139) Band 3 acts as a transporter for anions and glucose and additionally plays a role structurally by interacting with ankyrin and band 4.2. (140, 141) Additionally band 3 has a higher molecular weight, is less mobile and has tighter connections to ankyrin in comparison to band 3 in humans. (137, 139, 142)

When viewing the membrane as a whole, the surface-to volume ratio is one third of that which is physiological in humans, which reduces deformability. (139)

However, a higher stability of the membrane may be needed to withstand severe changes in osmolality during de-/ and rehydration. (133) The prize to pay is a reduced RBC deformability. A camel RBC will need more stress input to deform and therefore, the threshold for the tumbling-to-rolling transition shifts to higher blood flows. The viscosity contrast in dromedaries is also quite high since the MCHC is about 47.7 g/dL and the plasma viscosity ranges from 1.01 to 1.10 mPa*s (1), which means that cells and plasma do not couple, and RBCs flow as separate entities which lead to their friction in the vessels. This elevates blood viscosity although RBC aggregation is absent.

1.3.5.1. Racing camels

Although free-ranging camels do not run, except when males are in rut, (1) camels are able to perform high intensity exercises when they are chased. Camel racing developed out of a traditional practice and has become a popular and profitable sport in the countries of the Arabian Peninsula, North Africa, Horn of Africa, Pakistan, Mongolia and Australia. (143) Exercise is usually associated with a transient increase of the RBC count, but against expectations, racing camels sometimes suffer from a low HCT of unknown origin and are treated by iron supplementations or blood transfusion (1, 144) This decrease of the HCT is more obvious if the animal is infected with blood parasites. (145) Apart from the risk of transfusion reactions and the transmission of infectious diseases, a blood transfusion always elevates blood viscosity and therefore the vascular resistance (146). An elevation of HCT could be of greater importance for blood flow in camels than in humans. The elliptic camel RBCs do not align in the flow streamlines but perform several uncoordinated motions like tumbling, flipping, and kayaking. When the hydrodynamic pressure in the blood vessels does not force their orientation, the cells approach in various spatial orientations in front of bifurcations or at distinct vascular curvatures and could crowd there. Blood flow will be locally impaired and RBCs might be even excluded from entering into smaller vessels. The unique behaviour of camel blood suspensions in rheometry (1) indicates, that blood viscosity

and wall shear stress is pronounced in vessels of high shear flow (e.g., small arteries and arterioles). This might limit the exercise performance of the animals, although the high HCT would improve the oxygen supply to the muscles. On the long term it might also cause vascular remodelling.

2. Study goal and design

It is unclear if the blood of Bactrian camels has the same characteristics as the blood of dromedary camels.

Since both camels seem to have similar hematological reference values and they originate from deserts, which entail a dry environment and extreme temperature changes, one might assume that the hemorheological properties are similar. As in the dromedary camel, the viscosity of Bactrian camel blood might not severely change with temperature changes, and since the RBC membrane stability is high (1), this must result in less RBC deformability and low viscosity fluctuations at different shear rates. However, the general characteristic can be different because Bactrian camels often live in regions subjected to more seasonal temperature fluctuations at higher altitude. Moreover, the blood of the Bactrian camels studied in this diploma thesis was obtained in Austria from animals of both genders from two small herds during summer, while the dromedary camel blood was acquired in Dubai from female camels of one big herd during spring. The conditions are therefore more diverse for the Bactrian camel group, because of the influences of herd and sex. In contrast blood from dromedary camels was withdrawn in the rutting season and might have had variability in the hormonal status.

To determine differences between Bactrian camel blood and dromedary camel, the following questions will be answered:

1) Is the blood viscosity different between Bactrian and dromedary camels?
2) Does the temperature dependency of whole blood viscosity differ between Bactrian and dromedary camels?
3) Is shear thinning improved in Bactrian camels compared to dromedary camels?

If all questions can be answered with a “no”, no difference exists in the blood behaviour of old-world camelids. Insight will also be provided in regard to hematological differences between the species that can influence the outcome. Since blood from the Bactrian camels was obtained in Austria during summer from two camel farms and since the dromedary camel blood was taken from a large herd in their native country, the study also includes two

different environments and lifestyles. If the blood behaviour is similar in both species, the environment does not affect it.

3. Methods and Materials

Blood samples

Venous blood was drawn via the jugular vein from nine clinically healthy Bactrian camels of both sexes (ethical clearance number: GZ: BMWFW-66.009/0230-WF/V/3b/2017) into 9 mL EDTA tubes (Vacutainersystem Greiner BioOne, Austria). The camels were housed in Lower Austria (two separate farms, farm 1: 3 animals; farm 2: 6 animals), had free access to a paddock, and were accustomed to their trainers/owners so that blood withdrawal (27-49 mL) was accomplished with minimal fixation of the animal's head and neck. No haircut was necessary due to sampling in the summer months (June – August). This procedure should reduce the animals' stress during blood withdrawal. Samples were cooled in insulated bags during the 1-2 hours of transportation to the laboratory. To draw comparisons to humans, blood from five healthy volunteers were included into the study as well (ethical clearance number 1892/2013). Blood was withdrawn from the antecubital vein into 9 mL EDTA tubes and tested within that day.

In the laboratory, a portion of 7 mL blood was removed from one tube and put aside to measure blood at its native HCT. The remaining tubes were centrifuged at room temperature (1500 *g*, 3 minutes) and the plasma and cellular component were combined in two separate tubes. Afterwards, the HCT of the RBC concentrate was determined (hematocrit centrifuge, Hettich, Germany). Using the following formula: $c_1 * v_1 = c_2 * v_2$ the mixing ratio of plasma and RBC concentrate was defined to produce 7 mL portions with different HCT values (plasma, 30%, 40%, 50%, 60%, 70%; there was not enough blood drawn from each camel to generate the samples with higher HCT values from each individual). The HCT in each sample was controlled again to assure correct mixing of plasma and RBC concentrate.

Rheometry

The samples were immediately analysed using the Physica MCR302 rheometer (Anton Paar, Austria). 3.2 mL of each sample was placed in the stainless steel double gap cylinder system (internal gap: 0.417mm; external gap: 0.462mm, cup length: 42mm). After a 30 s pre-shear interval at 300 s^{-1} six flow curves were performed in subsequent order. Flow curves started with the highest applied strain rate (1000 s^{-1}) and ended at the lowest one (10 s^{-1}), having nine measuring points in-between on a logarithmic ramp. The first flow curve was performed at

42°C. After temperature equilibration flow curves were repeated at several temperatures (37°C, 32°C, 27°C, 22 °C, 17°C) always following a pre-shear interval (3 s, 300 s^{-1}) prior to each new flow curve. The viscosity was calculated by the Rheocompass™ software (version 1.19.335, Anton Paar, Austria) and using that data, the shear thinning was calculated by subtracting the viscosity at 1000s^{-1} from the viscosity at 10s^{-1}. The obtained data was compared to the blood of dromedary camels (1).

Other laboratory tests

All Bactrian camels had blood sent to a veterinary clinical laboratory (In-vitro GmbH, Vienna, Austria) to obtain a complete blood count (CBC) with differential.

3.1. Parameters

The nine data points on the flow curves display viscosity at the following shear rates: 10s^{-1}, 15.8s^{-1}, 25.1s^{-1}, 39.8s^{-1}, 63.1s^{-1}, 100s^{-1}, 158s^{-1}, 251s^{-1}, 398s^{-1}, 631s^{-1} and 1000s^{-1}. Due to the fact that samples were measured at different temperatures (12°C, 17°C, 22°C, 27°C, 32°C, 37°C, 42°C) and HCT values (native HCT, plasma (=0%), 30%, 40%, 50%, 60%, 70%, note that high HCT values are inconsistent), a mean sum of 352 viscosity vales were obtained from each camel. From this bulk of data only the viscosity value at 10 s^{-1} and 1000 s^{-1} shear rate and 40% HCT was used for the species comparison to answer questions 1 and 2 posed above. To also compare the behaviour of blood out of the full range of shear rates, shear thinning was calculated at each temperature and HCT. For species comparison only shear thinning at 12°C and 42°C temp and 40% HCT was used in order to answer question 3.

Sex, age and a CBC with differential was used to deduce reasons for possible viscosity outliers within the group of Bactrian camels.

***Table 2*: Overview table of the obtained variables (Source: own construction)**

Variable	Category	Type of variable
Camel number	in numbers	scale
Species	Bactrian camel/dromedary camel/human	nominal
Gender	male/female	nominal
Age	in numbers	scale
Hematocrit	in numbers	scale
Native hematocrit	yes/no	nominal
Temperature	in numbers	scale
Shear rate	in numbers	scale
Viscosity	in numbers	scale
Shear thinning	in numbers	scale

([Viscosity at $10s^{-1}$] – [Viscosity at $1000s^{-1}$])		
Red blood cells	in numbers	scale
Haemoglobin	in numbers	scale
MCV	in numbers	scale
MCHC	in numbers	scale
Leucocytes	in numbers	scale
Band neutrophils	in numbers	scale
Segmented neutrophils	in numbers	scale
Lymphocytes	in numbers	scale
Monocytes	in numbers	scale
Eosinophils	in numbers	scale

3.2. Statistical analysis

The statistical analysis was executed by using IBM SPSS® Statistics (version 25) to answer the three questioned posed above (see 2. Study goal and design):

1. The Mann-Whitney *U* test was used to evaluate if there is a significant difference in blood viscosity between Bactrian and dromedary camels. Viscosity values at $10s^{-1}$ and $1000s^{-1}$ shear rates, 40% HCT and 37°C were compared
2. Linear regression was used to compare the temperature dependency at 40% HCT and $10s^{-1}$ and $1000s^{-1}$ shear rates between Bactrian and dromedary camels
3. The Independent Sample *t*-test was used to compare the shear thinning between Bactrian and dromedary camels. For the comparison of the temperature dependency of shear thinning, a paired *t*-test was applied to the data of both camels (12°C and 42°C) as well as to the human data (12°C and 37°C).

A p-value ≤ 0.05 would either significantly show a difference between compared values or an influence of one parameter on another,

In the following, the data of Bactrian camels, dromedary camels and humans will be presented in tables (showing: mean values and standard deviation (SD) of viscosity; mean, variance, standard deviation, minimum, maximum and interquartile ranges of the shear thinning; mean, maximum and minimum values of the CBC with differentials) and graphically by line graphs (showing mean viscosity) and box plots (showing shear thinning).

The statistical analysis will rule out one of the following hypotheses:

Null hypothesis: Old World camelid blood has similar hemorheological properties.

Alternative hypothesis: The hemorheological properties of Bactrian camel blood differ from the blood of dromedary camels.

4. Results

Both male and female Bactrian camels are represented with ages ranging from 1 to 22 years. The results are compared to the blood of ten dromedary camels from Dubai and are all female camels bred for racing purposes, and five humans.

Due to limited constraint of the camels during blood withdrawal, there was not enough blood available to generate all HCT dilutions. Statistics referring to a HCT at 40% contain results from 8 camels, while the HCT values at 30% and 50% contain results from 6 camels and measurements at a HCT of 60% could only take place in 4 camels.

One technical problem arouse with one camel sample. Here, mixing of plasma and RBC concentrate for a hematocrit of 30% was incorrect (HCT was too low). Calculation errors and a wrong measurement of the RBC concentrate HCT were excluded after double-checking – it is probable that the pipette used for this camel was defective. After switching pipettes, a sample at 20% HCT was produced since there was not enough RBC concentrate left to produce a HCT of 30%. Except for this case no other difficulties in producing the different HCT values occurred.

Another technical problem occurred during the rheological test of the native blood sample from two camels. The automated test stopped while measuring at low temperatures (12°C, 17°C); all other measurements before that stop (42°C – 22°C) could be fully completed.

4.1. Viscosity differences between Bactrian and dromedary camels

At both $1000s^{-1}$ ($p = 1.000$) and $10s^{-1}$ ($p = 0.105$) no significant difference was observed in the viscosity values of the two species. However, at a shear rate of $10s^{-1}$ the mean viscosity value tended to be higher in Bactrian camels (see the line graphs below; figures 13 – 18).

In comparison to the blood of the camels, the human blood had a higher viscosity at lower HCT values and the shear thinning behaviour is more pronounced. However, at high shear rates, viscosity became lower as the HCT increased. (see figures 13 – 18, tables 3 – 5)

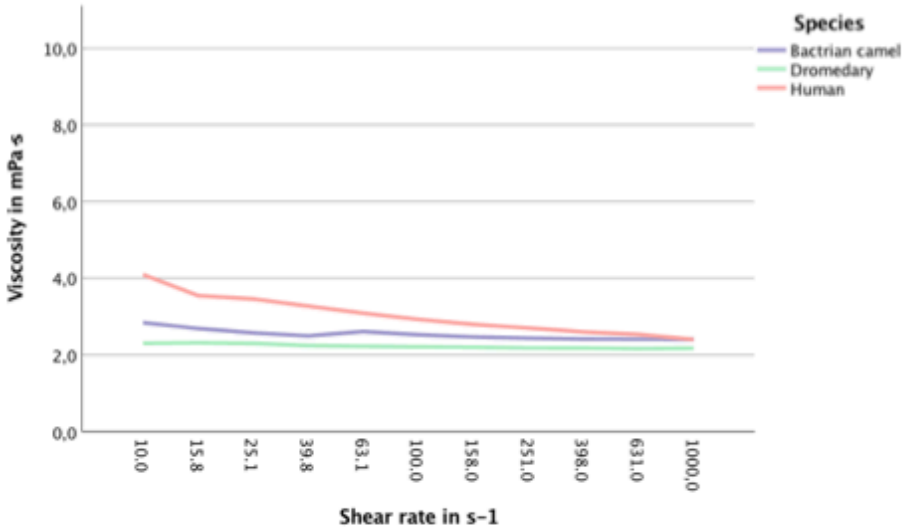

Figure 13: Mean value line graphs at 37°C and 30% HCT (Source: own construction)

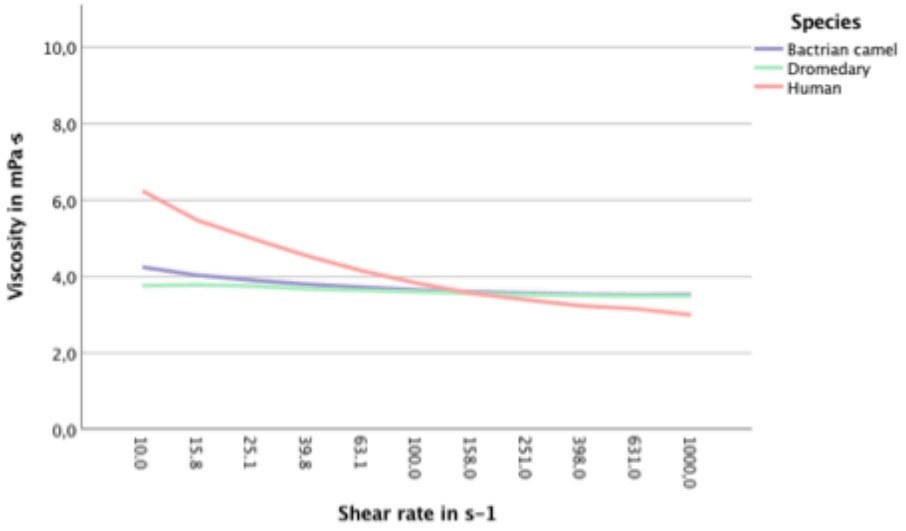

Figure 14: Mean value line graphs at 37°C and 40% HCT (Source: own construction)

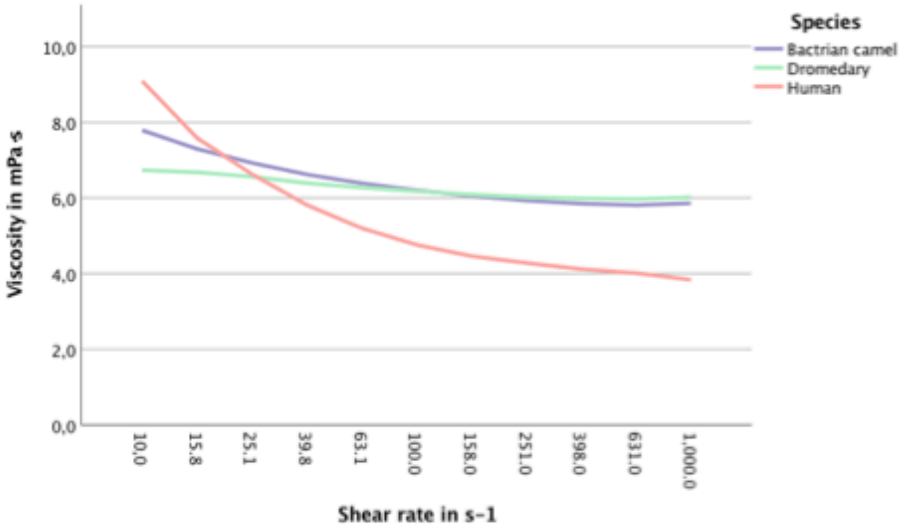

Figure 15: Mean value line graphs at 37°C and 50% HCT (Source: own construction)

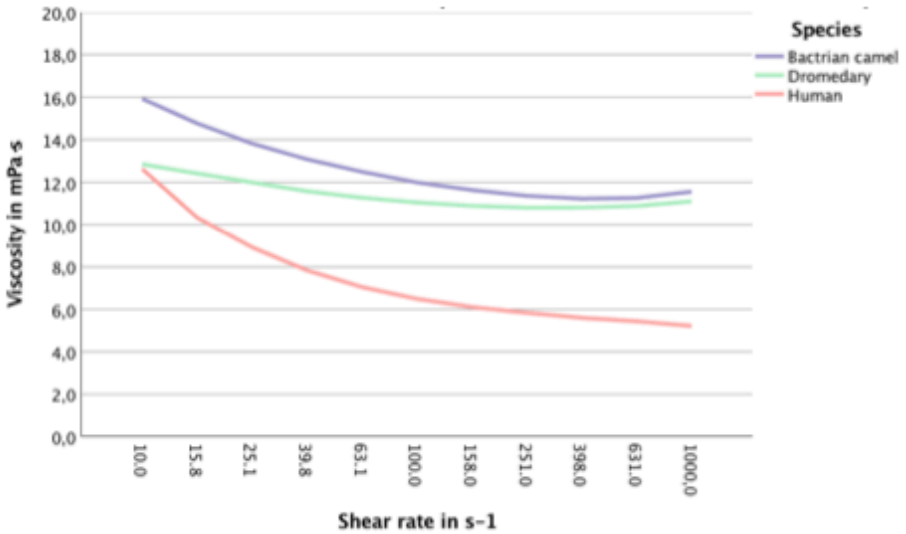

Figure 16: Mean value line graphs at 37°C and 60% HCT (Source: own construction)

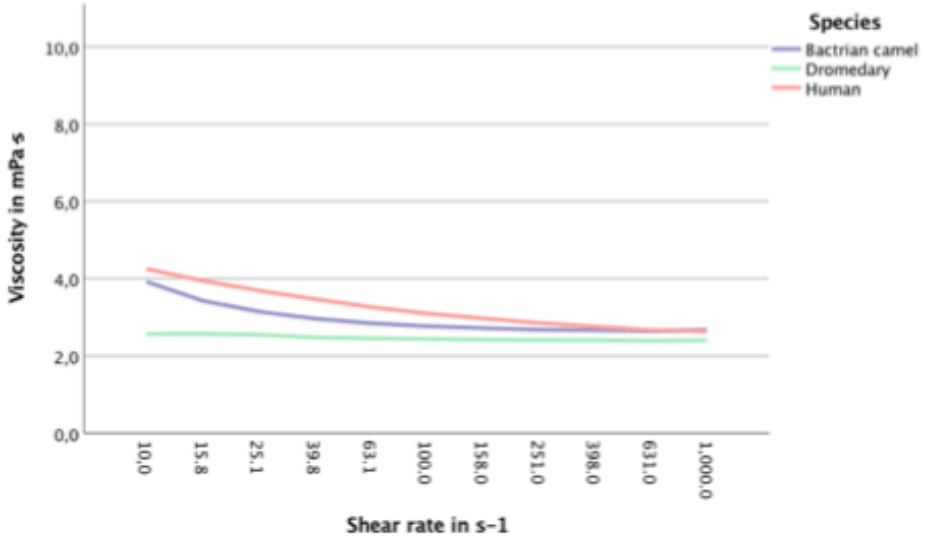

Figure 17: **Mean value line graphs at a HCT of 30% and at 32°C (Source: own construction)**

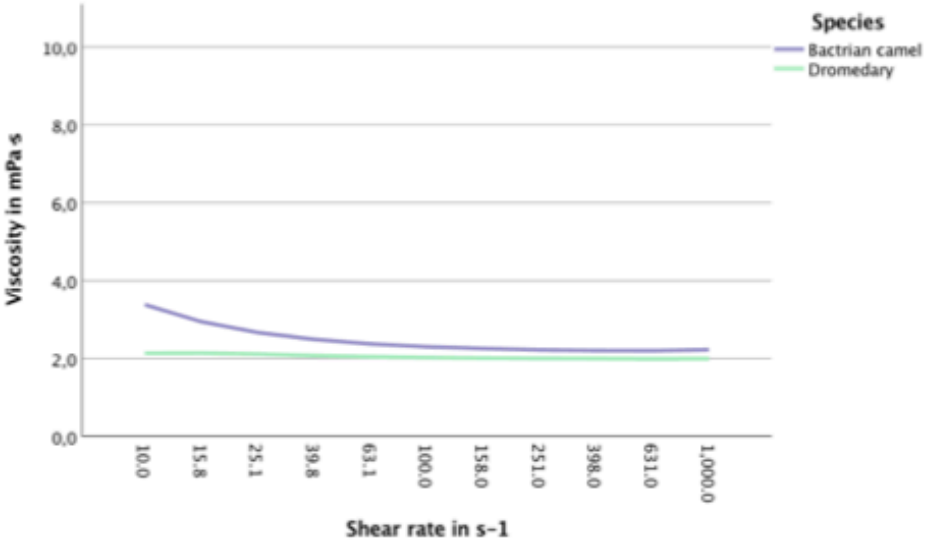

Figure 18: **Mean value line graphs at a HCT of 30% and at 42°C (no data for humans) (Source: own construction)**

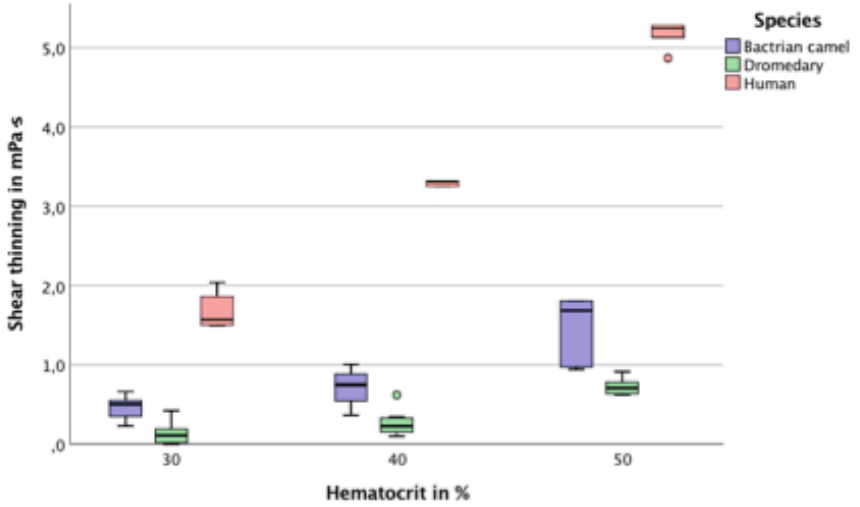

Figure 19: **Boxplot showing shear thinning at 37°C with varying HCT values (Source: own construction)**

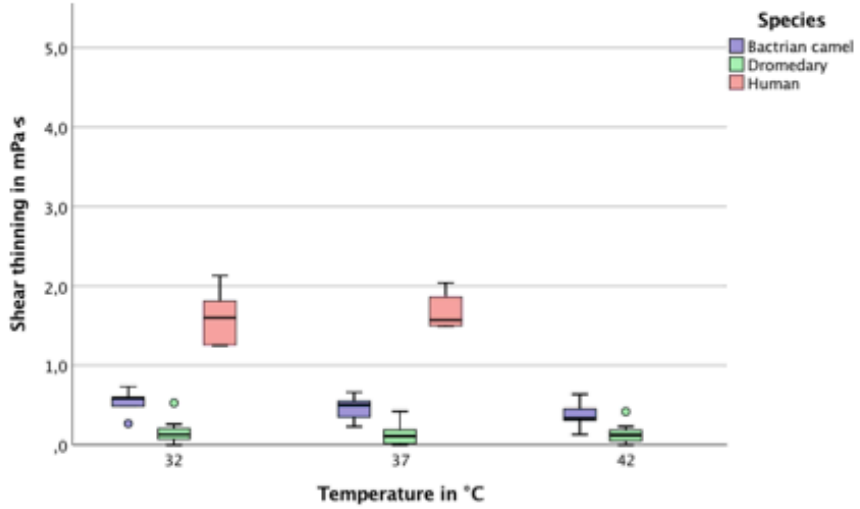

Figure 20: **Boxplot showing shear thinning at 30% HCT with varying temperatures (Source: own construction)**

***Table 3*: Mean viscosity depending on the HCT, the temperature and the shear rate - Bactrian camel (Source: own construction)**

Hematocrit	Temperature	Shear rate of $10s^{-1}$		Shear rate of $1000s^{-1}$	
		Mean Viscosity in mPa*s	Standard deviation	Mean Viscosity in mPa*s	Standard deviation
30%	32°C	3.92	1.83	2.67	0.26
	37°C	3.84	2.46	2.40	0.21
	42°C	3.38	1.97	2.23	0.22
40%	37°C	4.25	0.55	3.53	0.38
50%	37°C	7.79	1.54	5.86	0.44
Plasma	37°C	1.59	0.23	1.15	0.07

***Table 4:* Mean viscosity depending on the HCT, the temperature and the shear rate - Dromedary camel (Source: own construction)**

Hematocrit	Temperature	Shear rate of $10s^{-1}$		Shear rate of $1000s^{-1}$	
		Mean Viscosity in mPa*s	Standard deviation	Mean Viscosity in mPa*s	Standard deviation
30%	32°C	2.57	0.20	2.40	0.07
	37°C	2.30	0.18	2.17	0.07
	42°C	2.14	0.17	1.99	0.06
40%	37°C	3.77	0.26	3.50	0.16
50%	37°C	6.74	0.32	6.02	0.31
Plasma	37°C	1.10	0.10	1.01	0.03

***Table 5*: Mean viscosity depending on the HCT, the temperature and the shear rate – Human (Source: own construction)**

Hematocrit	Temperature	Shear rate of $10s^{-1}$		Shear rate of $1000s^{-1}$	
		Mean Viscosity in mPa*s	Standard deviation	Mean Viscosity in mPa*s	Standard deviation
30%	32°C	4.25	0.40	2.64	0.10
	37°C	4.09	0.33	2.40	0.12
	42°C	no data	no data	no data	no data
40%	37°C	6.24	0.26	2.99	0.18
50%	37°C	9.09	0.48	3.84	0.24
Plasma	37°C	no data	no data	no data	no data

4.2. Temperature dependency of blood viscosity

The temperature dependency of blood viscosity was analysed (at 40% HCT) at both shear rates of $1000s^{-1}$ and $10s^{-1}$ using linear regression. In both species a significant dependency on the temperature could be observed ($p < 0.001$). The coefficients of determination (R^2) are

shown below (see table 6). A difference in dependency could not be determined as the coefficients in the linear regression equations were similar in both species. (see table 7)

***Table 6*: Coefficient of determination in Bactrian and dromedary camels at different shear rates (40% HCT) (Source: own construction)**

	Coefficient of determination (R^2)	
	Shear rate of $1000s^{-1}$	Shear rate of $10s^{-1}$
Bactrian Camel	0.823	0.598
Dromedary Camel	0.929	0.865

***Table 7*: Regression coefficient in Bactrian and dromedary camels at different shear rates (40% HCT) (Source: own construction)**

	Regression coefficient	
	Shear rate of $1000s^{-1}$	Shear rate of $10s^{-1}$
Bactrian Camel	-0.124	-0.189
Dromedary Camel	-0.120	-0.126

4.3. Shear thinning

The shear thinning values were first compared between Bactrian and dromedary camels to show inter-species differences. This was achieved by performing an Independent Samples *t*-test (40% HCT, 37°C), which showed a significant difference in the shear thinning values ($p = 0.001$). The Bactrian camels showed higher values than the dromedary camels. To examine the temperature dependency of shear thinning, a paired *t*-test was performed within the species themselves by comparing the shear thinning at 42°C and 12°C. The Bactrian camels showed a significant difference as the temperature changed ($p = 0.047$) with the shear thinning decreasing as the temperature increased. However, the shear thinning was unaffected by temperature in the dromedary camels ($p = 0.190$).

For comparison, shear thinning is much higher in human blood compared to both camelids at both, 37°C and 12°C ($p < 0.001$). (see figures 19 and 20, as well as table 8 and 9)

***Table 8*: Shear thinning depending on the HCT (at a temperature of 37°C) (Source: own construction):**

Hematocrit		Human	Dromedary	Bactrian camel
30%	Mean	1.692000	0.129075	0.458880
	Variance	0.060	0.021	0.029
	Standard deviation	0.2459065	0.1434941	0.1704551
	Minimum	1.4900	-0.0258	0.2296
	Maximum	2.0400	0.4222	0.6617
	Interquartile range	0.4550	0.1823	0.3167
40%	Mean	3.246000	0.267662	0.714875
	Variance	0.015	0.028	0.051
	Standard deviation	0.1242176	0.1685232	0.2267019

	Minimum	3.0300	0.0980	0.3637
	Maximum	3.3200	0.6203	1.0062
	Interquartile range	0.1800	0.1875	0.4257
50%	Mean	5.254000	0.722450	1.418060
	Variance	0.100	0.010	0.180
	Standard deviation	0.3161171	0.1020905	0.4242094
	Minimum	4.8700	0.6202	0.9414
	Maximum	5.7400	0.9121	1.8052
	Interquartile range	0.5100	0.1491	0.8053

***Table 9*: Shear thinning depending on the temperature (at a HCT of 40%) (Source: own construction):**

Temperature		Human	Dromedary	Bactrian camel
32°C	Mean	3.302000	0.259350	0.791063
	Variance	0.047	0.029	0.077
	Standard deviation	0.2159167	0.1713115	0.2778578
	Minimum	3.0300	0.1045	0.4045
	Maximum	3.5600	0.6216	1.2273
	Interquartile range	0.4050	0.1848	0.4939
42°C	Mean	no data	0.345850	0.622212
	Variance	no data	0.021	0.034
	Standard deviation	no data	0.1448093	0.1851651
	Minimum	no data	0.1485	0.3677
	Maximum	no data	0.5885	0.8863
	Interquartile range	no data	0.2253	0.3609

4.4. CBC with differential

The CBC results were similar to the reference intervals given by Vap et al. (129), although they tended to be a little lower. This could be expected as there were speculations that the intervals may be lower in Old World camels. The only two exceptions to this were the MCV and the leucocytes, which had a slightly higher count. While viewing the blood results of the camels individually, it was noticeable, that there was a difference depending on where the camels lived. The blood was sampled from two separate camel farms. All three camels from one of the farms had lower counts of leucocytes, 11 to 12.5 G/L, but higher counts in eosinophils ranging from 13 to 21%. On the other farm the leucocytes ranged from 12.5 to 22 G/L and the camel with the highest value of eosinophils had a count of 6%. Thus these camels had higher percentages among the other differential values, especially among the lymphocytes. Otherwise no significant other differences were visible.

In comparison to human reference values, the HCT was lower in the camels, whereas the RBC count was much higher while the MCV is significantly lower. Camels had more

leucocytes than humans and the count in eosinophils was increased. However, when comparing the count of the camels from the farm with the lower values, the difference to humans was just marginally noticeable.

***Table 10*: Mean values and the minimum and maximal value of the CBC with differentials (Source: own construction)**

	Mean	Minimum - Maximum
HCT (%)	28.78	25 – 34
RBC (T/L)	9.95	8.56 – 11.35
Hb (g/dL)	12.56	10.70 – 14.10
MCV (fL)	28.98	26.70 – 34.10
MCHC (g/dL)	31.00	30 – 32
WBC (G/L)	14.33	11.38 – 21.97
Band neutrophils (%)	5.86	1 – 15
Segmented neutrophils (%)	61.89	52 – 71
Lymphocytes (%)	21.00	11 – 40
Monocytes (%)	3.44	1 – 6
Eosinophils (%)	9.11	1 – 21

4.5. Outliers

The viscosity value in one camel's samples at HCT values of 30%, 50% and 60% were abnormal in comparison to the other camels. At high shear rates the viscosity was similar to the other camels, but when the shear rate decreased, the viscosity increased notably more in comparison (e.g. at 30% HCT and at a shear rate of $10s^{-1}$ the viscosity in this camel was 8.81 mPa*s, while the mean viscosity was 2.84 mPa*s). Only the measurements of plasma and at a HCT of 40% were similar to the other camels' measurements. This was a 22-year-old non-pregnant female camel. Her CBC with differentials was inconspicuous and she was clinically healthy and had no known illnesses before. She was the oldest camel, however, the second oldest was only two years younger and did not show such tendencies.

4.6. Conclusion

Questions 1 and 2 (see 2. Study goal and design) can be answered with a "no":

- Blood viscosity is not significantly different between Bactrian and dromedary camels
- The temperature dependency of blood viscosity is similar in Bactrian and dromedary camels

However, question 3 cannot be answered with a "no". Shear thinning is higher in Bactrian camels compared to dromedary camels, albeit still low in comparison to human blood.

Furthermore, shear thinning depended on the test temperature, since it decreased in Bactrian camels as the temperature was raised, while it stayed constant in dromedary camels.

The null hypothesis can be discarded since not all questions could be answered with a "no" and thus we can assume that the hemorheological properties of Bactrian camel blood differs from the hemorheological properties of dromedary camel blood.

5. Discussion

This study was designed to investigate the rheological properties of Bactrian camel blood in order to explore differences between Old World camelids. Camel blood was also selected as the study material because of the unique RBC flow behaviour (1). Unlike human RBCs, camel RBCs maintain their elliptic shape when they pass 10 μm rectangular capillaries or when they are flowed in a narrow slit in microfluidics. The microfluidic observations are confirmed by ectacytometry. Human RBCs typically take different shapes like slippers or parachutes at the same conditions. A slight change towards a more rounded shape in camel RBCs can only be generated by lowering the osmolality of the suspending medium. The fixed shape can be attributed to a stiff membrane, and indeed, single cell spectroscopy showed that apparent Young's modulus of Bactrian camel RBCs is more than threefold compared to human RBCs (147). The fixed shape in flow makes it possible to investigate the influence of viscosity contrast on blood viscosity. The viscosity contrast influences the motions a RBC can undergo. If RBCs align to the flow streamlines through coupling with the flowing plasma, this lowers blood viscosity. A high viscosity contrast hinders coupling and makes the behaviour of RBCs independent from each other. This results in Newtonian behaviour. The viscosity contrast rises if MCHC is high whereas at the same time plasma viscosity is low. Since MCHC is different between Old World camelids, the viscosity contrast might vary between the two species, too. If the plasma - RBC interaction were facilitated in Bactrian camels one would expect some higher extent of shear thinning. The second aim of this study was therefore to investigate the influence of MCHC on the flow behaviour of RBCs without changing simultaneously the size and shape of the cell.

Bactrian camel blood was comparable to dromedary camel blood by looking separately at the blood viscosity values at low and high shear rates ($p = 0.105$ at $10s^{-1}$ and $p = 1.000$ at $1000\ s^{-1}$), as well as on their temperature dependency. However, when the differences in viscosity that were indeed visible (see figures 13 – 20) were connected to a single term (to shear thinning), one can no more conclude that both blood suspensions possess identical

behaviours. The differences are subtle and could stem from environmental factors that generate a phenotypic shift since the Bactrian camels lived in Austria and thus were subjected to a milder climate compared to the dromedary camels studied in Dubai. Another difference between the study groups is that the Bactrian camels were a more heterogeneous group with ages from 1 to 22, both sexes being represented, as well as the animals originating from two separate farms. However, none of these factors seemed to influence the viscosity in a particular direction when comparing the Bactrian camels individually to each other, so there is no reason to assume that the heterogeneity of the Bactrian camels is cause for the difference in shear thinning between dromedary and Bactrian camels. Selective studies would have to take place to determine if these differences are generally present in Bactrian and dromedary camels or if the environment caused these changes.

Comparative studies by using blood of different species also help to gain an insight into pathophysiological mechanisms. The results of this diploma thesis support the importance of the viscosity contrast for RBC flow. The viscosity contrast is expected to be lower in the Bactrian camels, with a mean plasma viscosity of 1.15 – 1.59 mPa*s (at 37°C) and a MCHC of 30 – 32 mg/dL, compared to the dromedary camels, which had a plasma viscosity of 1.01 – 1.10 mPa*s (at 37°C) and MCHC of even 47.7 g/dL. The Bactrian camels with the lower contrast showed higher values of shear thinning, and shear thinning also depended on the test temperature. In dromedary camels shear thinning was almost abolished and there was no temperature dependency found.

The clinical relevance of the study outcome is based on the HCT-dependency of camel blood viscosity. Despite camels having physiologically lower HCT values, one can assume that homologous blood transfusions prior to camel racing will raise the HCT unnaturally. Thus, it would be beneficial to know what the possible consequences of these practices are. Figure 16 shows the increase in viscosity at 60% HCT. Blood viscosity is doubled at high shear rates in Bactrian camels, but unexpectedly still higher at low shear rate compared to human. This can eventually cause symptoms of the hyperviscosity syndrome or cardiovascular remodelling due to an increase in wall shear stress (148, 149), which should be cause enough to think critically about such practices in camels.

Keeping camels healthy and thus protecting these intriguing animals is also of importance for humanity, since camels are used to living in deserts with limited access to water and can endure temperatures from 20°C to 40°C, which makes them a viable resource for milk, meat, leather and wool in a world confronted with climate change. (150)

Limiting factors of this study include the low number of camels tested (9 camels with one camel showing abnormal viscosity values), the difficulty in drawing enough blood from each camel to provide all HCT values described above and the different environments as well as lifestyles in-between the dromedary and Bactrian camel groups, which may cause hemorheological differences aside from differences in the species themselves.

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7. List of abbreviations

CBC	Complete blood count
EDTA	Ethylenediaminetetraacetic acid
Hb	Haemoglobin
HCT	Hematocrit
LH	Luteinizing Hormone
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
RBC	Red blood cell
WBC	White blood cell

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