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Magnetic susceptibility of fresh whole human blood

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The volume magnetic susceptibility of fresh whole human blood was measured using vibration magnetometry. Using a simple mathematical model, the difference in volume magnetic susceptibility between completely deoxygenated and completely oxygenated erythrocytes was estimated. The found value $\Delta\chi_{do} = 0.28 \cdot 10^{-6}$ is of primary importance in mathematical algorithms for constructing MRI images and quantitative assessment of blood oxygen saturation.

Keywords: human whole blood, volume magnetic susceptibility.

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More than one hundred and fifty years ago, on November 8, 1845, Faraday has been investigating the magnetic properties of dried blood and made a note: „Need to examine fresh liquid blood“ [1]. Had he determined the magnetic susceptibility of arterial and venous blood, he would have found that they differ greatly (by as much as 20 % for completely oxygenated and completely deoxygenated blood). This discovery, which had been made more than ninety years later by Pauling and Coryell, has undoubtedly aroused great interest and affected significantly the course of research into blood and hemoglobin. In 1936, Pauling and Coryell have reported the diamagnetic susceptibility of oxyhemoglobin (i. e., oxygenated blood) and the paramagnetic susceptibility of deoxyhemoglobin (i. e., deoxygenated blood) [2]. These studies have provided an opportunity to estimate, among other things, the magnitude of effective magnetic moments of Fe^{2+} ions in hemoglobin. Many years later, in the present day, in-depth data on the magnetic properties of human blood are not of academic interest only, but are also essential for magnetic resonance imaging (MRI) [3,4]. In recent years, MRI methods have been used in a number of studies to evaluate the level of blood oxygen saturation with account for the difference in volume magnetic susceptibility between completely oxygenated and deoxygenated blood $\Delta\chi_{do}$ [4]. However, earlier studies have often relied on two very different values of $\Delta\chi_{do} = 0.18 \cdot 10^{-6}$ and $0.27 \cdot 10^{-6}$ [5,6], which led to significantly different oxygen saturation estimates. MRI measurements of oxygen saturation have recently been used to assess the oxygen extraction fraction and cerebral oxygen metabolism [7]. Since the reliability of these results depends directly on the accuracy of determination of venous oxygen saturation, it is crucial to obtain a correct $\Delta\chi_{do}$ value. Although this constant has been estimated in different ways in several previous studies, there appears to be no consensus on its actual value. The aim of the present study was to measure accurately the value of $\Delta\chi_{do}$ using the direct method of vibration magnetometry in order to determine the most reliable of the above values of magnetic susceptibility difference.

Fresh whole venous blood from a healthy 41-year-old man following a healthy lifestyle was used in experiments. A clinical blood analysis was performed before the measurements at the Center for Molecular Diagnostics. Anticoagulants were used in the process of blood sampling. A blood sample of a known volume ($0.09\,\text{cm}^3$) was placed in a polyethylene bag and sealed (Fig. 1). The dependences of magnetic moment on temperature $m(T)$ and magnetic field strength $m(H)$ of the samples were recorded using a vibration magnetometer of a Cryogen Free Measurement System (CFMS) produced by Cryogenic Ltd, UK. Dependence $m(T)$ was measured within the $T = 100-300\,\text{K}$ temperature range in a constant magnetic field with strength $H = 5\,\text{kOe}$. The magnetic moment of the samples was corrected for the diamagnetic contribution of the sample holder and the anticoagulant. The obtained magnetic moment value was converted into volume magnetic susceptibility χ_{blood} of fresh whole venous human blood (Fig. 2) in accordance with the following formula: $\chi_{blood} = m/(HV)$, where V is the sample volume in cm^3.

The curve shown in Fig. 2 is typical of diamagnetic materials, since the value of χ is negative. The plot still reveals a weak temperature dependence (the paramagnetic contribution is evident). It was demonstrated in [8] that the magnetic susceptibility of living tissues depends on temperature. Thus, the results do not contradict earlier data. It is evident that temperature variations of the measured χ_{blood} value within the range from $-0.71 \cdot 10^{-6}$ to $-0.67 \cdot 10^{-6}$ should affect the accuracy of the obtained $\Delta\chi_{do}$ value. Therefore, we resorted to a different type

Figure 1. Sample of fresh whole venous human blood of a known volume that was prepared for measurements: placed in a polyethylene bag and sealed.

of experiment: measurements of the magnetic moment at a given room temperature in magnetic fields of different strengths. Dependence $m(H)$ was measured in magnetic fields with strength up to $H = 50\,\text{kOe}$ in 100 Oe steps at temperature $T = 300\,\text{K}$ and was converted into volume magnetization (Fig. 3). The curve shown in Fig. 3 is also typical of diamagnetic materials, since the value of χ is negative (negative magnetization) and dependence $M(H)$ is linear with a negative slope. Strong magnetic fields ensure high quality of the experiment. In such experiments, χ is the slope coefficient of straight line $M(H)$. Thus, it may be determined by fitting the experimental curve with theoretical expression $M = \chi H$, which is what was done here. The χ_{blood} value determined this way was $-0.69 \cdot 10^{-6}$ with an accuracy no worse than $\pm 0.01 \cdot 10^{-6}$. This is the reason why the latter value is used in further analysis, discussion, and determination of $\Delta\chi_{do}$.

Volume magnetic susceptibility χ_{blood} of fresh whole blood is determined by contributions χ_{RBC} from red blood cells (erythrocytes) and χ_{plasma} from plasma (liquid intercellular matter): $\chi_{blood} = HTC \cdot \chi_{RBC} + (1 - HTC)\chi_{plasma}$ [6]. The contribution of paramagnetic dissolved oxygen O_2 to the overall susceptibility is minor and is neglected. Here, $HTC = 0.442$ is the hematocrit (ratio of the volume of red blood cells (erythrocytes) to the total blood volume). Magnetic susceptibility of blood plasma χ_{plasma} may be estimated as the average between the magnetic susceptibilities of water (χ_{water}), which makes up $\sim 95\,\%$ of the volume of liquid intercellular matter, and dry matter (mostly protein) ($\chi_{protein}$), which makes up 5 % of the volume. Thus, $\chi_{plasma} = 0.95\chi_{water} + 0.05\chi_{protein}$. The volume magnetic susceptibility of water is $\chi_{water} = -0.72 \cdot 10^{-6}$. It has already been demonstrated that various non-paramagnetic metal-containing and metal-free proteins have the same magnetic susceptibility

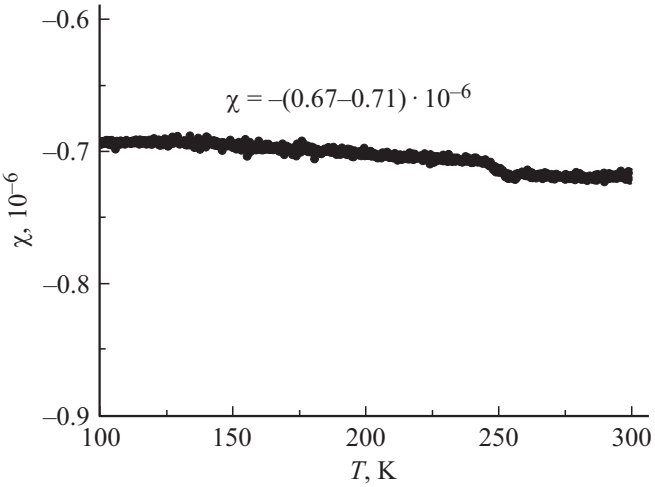

Figure 2. Temperature dependence of magnetic susceptibility χ of fresh whole human blood measured in a 5 kOe magnetic field.

$\chi_{protein} = -0.78 \cdot 10^{-6}$. Using the values of volume magnetic susceptibilities of water χ_{water} and plasma protein $\chi_{protein}$ and taking their proportion in plasma into account, we obtained an estimate of $\chi_{plasma} = -0.72 \cdot 10^{-6}$. In turn, the magnetic susceptibility of red blood cells (χ_{RBC}) is specified by the contributions of two major components of an erythrocyte (water and hemoglobin): $\chi_{RBC} = (1 - k)\chi_{water} + k\chi_{\text{Hb}}$ [6]. Here, k is the volume fraction of hemoglobin in an erythrocyte and χ_{Hb} is the volume magnetic susceptibility of hemoglobin. Naturally, $k = (MCHC/MCH)MCV$. Here, $MCHC = 342\,\text{g/l}$ is the average concentration of hemoglobin in packed red blood cells, $MCH = 30.2\,\text{pg}$ is the average hemoglobin content of an individual erythrocyte, and $MCV = 88.3\,\text{fl}$ is the average volume of an erythrocyte in the studied

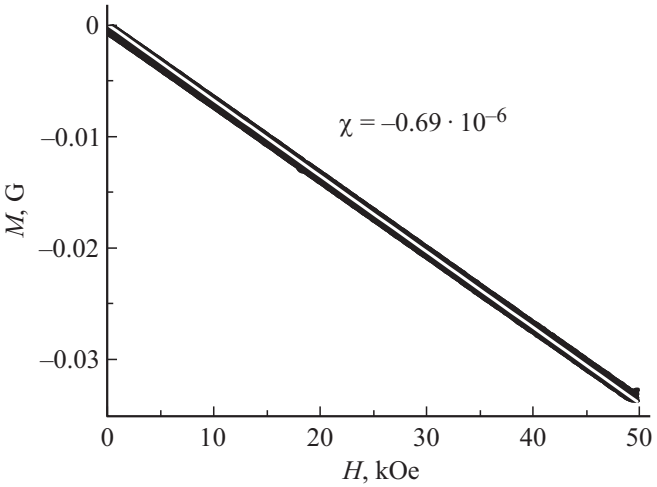

Figure 3. Dependence of magnetization of fresh whole human blood on the magnetic field strength measured at temperature $T = 300$ K. The solid white line represents the approximation by expression $M = \chi H$.

samples of fresh whole venous blood. In turn, the magnetic susceptibility of hemoglobin is specified by the diamagnetic oxyhemoglobin component (oxyHb) and the paramagnetic deoxyhemoglobin component ($deoxy$Hb): $\chi_{\text{Hb}} = \chi_{oxy\text{Hb}} + (1-s)\chi_{deoxy\text{Hb}}$ [6]. Diamagnetic oxyhemoglobin component $\chi_{oxy\text{Hb}}$ is essentially the volume magnetic susceptibility of hemoglobin in the low-spin state with $S = 0$ (i.e., simply protein): $\chi_{oxy\text{Hb}} = \chi_{protein}$. Paramagnetic deoxyhemoglobin component $\chi_{deoxy\text{Hb}}$ represents the volume magnetic susceptibility of hemoglobin in the high-spin state with $S = 2$. Thus, the expression for the magnetic susceptibility of red blood cells (χ_{RBC}) takes the following form: $\chi_{RBC} = (1-k)\chi_{water} + k[\chi_{protein} + (1-s)\chi_{deoxy\text{Hb}}]$ [6]. Here, s is the oxygen saturation, the fraction of oxygenated hemoglobin relative to total hemoglobin in the blood. Expanding the brackets in the last expression, we obtain

$$\chi_{RBC} = (1-k)\chi_{water} + k\chi_{protein} + k(1-s)\chi_{deoxy\text{Hb}}.$$

Since $\Delta\chi_{do} = \chi_{RBC,s=0} - \chi_{RBC,s=1} = k\chi_{deoxy\text{Hb}}$, we find $\chi_{RBC} = (1-k)\chi_{water} + k\chi_{protein} + (1-s)\Delta\chi_{do}$. It follows that

$$\Delta\chi_{do} = [\chi_{RBC} - (1-k)\chi_{water} - k\chi_{protein}]/(1-s).$$

Here, $\chi_{RBC} = [\chi_{blood} - (1-HTC)\chi_{plasma}]/HTC$. Estimating the value of

$$k = (MCHC/MCH)MCV$$

$$= (342[\text{g/l}]/30.2 \cdot 10^{-12}[\text{g}]) \cdot 88.3 \cdot 10^{-15}\ [\text{l}],$$

we find that it is equal to unity with an accuracy of up to five decimal places. The expression for $\Delta\chi_{do}$ is then simplified to $\Delta\chi_{do} = (\chi_{RBC} - \chi_{protein})/(1-s)$. Inserting the expression for χ_{RBC} into this formula, we obtain the end result:

$$\Delta\chi_{do} = \frac{\frac{\chi_{blood} - (1-HTC)\chi_{plasma}}{HTC} - \chi_{protein}}{1-s}.$$

The values of quantities found in the last expression were determined above or are known from literature. The value of $\chi_{blood} = -0.69 \cdot 10^{-6}$ was obtained in measurements with a vibration magnetometer. As was demonstrated above, $\chi_{plasma} \approx \chi_{water} = -0.72 \cdot 10^{-6}$. The value of $\chi_{protein} = -0.78 \cdot 10^{-6}$ is known from literature. Hematocrit $HTC = 0.442$ was determined via clinical blood analysis. The typical value of venous blood saturation is $s = 0.55$. Inserting the indicated values into the last formula, we obtain the following estimate of $\Delta\chi_{do}$:

$$\Delta\chi_{do} = 0.28 \cdot 10^{-6}.$$

Thus, the results of high-sensitivity vibration magnetometry measurements of magnetic susceptibility of fresh whole human blood and clinical blood analysis were used to determine the difference in volume magnetic susceptibility between completely deoxygenated and completely oxygenated erythrocytes. It turned out that this difference is $\Delta\chi_{do} = 0.28 \cdot 10^{-6}$. The obtained result is very close to the corresponding value of $\Delta\chi_{do} = 0.27 \cdot 10^{-6}$ measured by a different research group with a SQUID magnetometer and is noticeably higher than the value of $\Delta\chi_{do} = 0.18 \cdot 10^{-6}$, determined by measuring the magnetic susceptibility using the Faraday method. The observed discrepancies may be attributed to the higher accuracy of modern magnetometric methods. We note in conclusion that $\Delta\chi_{do}$ was measured at room temperature, since it was not possible to heat the sample to body temperature. The paramagnetic component of susceptibility is temperature-dependent, and the $\Delta\chi_{do}$ values may thus differ. However, this effect is expected to be marginal, since the difference in temperature between the two conditions and the concentration of paramagnetic elements are small.

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Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee

and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed voluntary consent was obtained from study participants.

Conflict of interest

The authors declare that they have no conflict of interest.

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