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Whole body bioimpedance as a mirror of the influence of hemorheological factors on electric properties of blood: a step forward with Hanai's mixture conductivity theory.

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Abstract

When electrical impedance (Z) is directly measured on blood, it is proportional to the number of red cells, their aggregation, and their changes in shape and alignment in response to changing stress forces, and is strongly correlated to hematocrit and blood viscosity. Whole body Z is correlated to hemorheologic parameters, but its correlation with hematocrit and whole blood viscosity is paradoxically negative. Recent developments of the interpretation of impedance analysis based on Hanai's mixture conductivity theory allows a more interpretative analysis of impedance in terms of resistance R and resistivity ρ of total body water, extracellular water (ECW) and intracellular water. We investigated relationships between blood rheology and these calculations of R and ρ in a sample of 83 subjects (age: 9-64 yr; BMI: 17-44 kg/m²). BIA was performed with a multifrequency bioelectrical impedancemeter using low intensity at the following frequencies: 1, 5, 10, 50 and 100 kHz. Viscometric measurements were done with a falling ball viscometer. Hematocrit was measured with microcentrifuge. RBC aggregability, that in the previous studies was not related to whole body impedance, despite its in vitro measurability with such measurements, was correlated to extracellular resistance and resistivity. The Myrenne index "M" was negatively correlated to the resistivity of ECW ρ_e (r=0.463). The SEFAM index "S10" is correlated to ρ_e (r=0.761). We found a new prediction of Quemada's viscometric index of RBC rigidity "k" (r=0,487). These correlations are consistent with the theoretical expectations, suggesting that a more in-depth analysis of electric properties of the whole body provides a closer approach of the influence of RBC rheology on blood electrical properties.

Keywords: impedance, resistance, resistivity, blood, red cell aggregation, hematocrit

1. Impedance of blood as a measurement of hemorheological parameters in vitro

Impedance (Z) is the frequency-dependent opposition of a conductor to the flow of an administered alternating current. This opposition has two components or vectors, termed resistance (R) and reactance (Xc), which are linked mathematically as:

$Z^2=R^2+X^2c$

R is the pure opposition of the conductor to the flow of current. Reactance is related to capacitance produced by tissue interfaces and by cell membranes. Capacitance causes the administered current to lag behind the voltage and creates a phase shift that is represented geometrically as the phase angle or arc tangent

of the ratio Xc/R.

The measurement of impedance of blood in vitro has been reported to reflect hemorheological parameters [1-11]. On the whole it appears that the number of red cells, their aggregation, and their changes in shape and alignment in response to changing stress forces modify the electric properties of blood. This relation is close enough to make bioimpedance a tool for the monitoring of hematocrit and RBC aggregation. When impedance is directly measured *in vivo* with electrodes inserted into the blood stream, it still exhibits strong positive correlations with hematocrit and blood viscosity [12-13]. On the whole, conductivity of blood is proportional to spatial average velocity of RBCs, so that blood resistivity is proportional to hematocrit, RBC aggregation, whole blood viscosity and RBC rigidity.

2. Whole body bioimpedance also correlates with hemorheological parameters

On the other hand, whole body bioimpedance is a widely employed method for assessing body composition, and more precisely the volumes of body fluids and the cellular mass. Therefore, we were interested over the last years in investigating to what extent whole body impedance measurements are also correlated to some hemorheologic factors as observed with blood impedance.

Surprisingly, quite strong correlations were repeatedly found in various samples, showing that whole blood viscosity and hematocrit were statistically related to whole body impedance [14-16].

Presumably, this finding is explained by the fact that determinants of blood rheology (plasma protein and ion composition, RBC shape) and determinants of electric properties of blood (charge carriers) are closely related. In addition, whole body impedance is related to body water status which is clearly a modifier of blood rheology. Although some of these correlations are logic and consistent with in vitro data, such as the positive correlation between RBC rigidity and impedance [17], others are still difficult to interpret.

3. Paradoxes

However, the biophysical basis of some of these correlations is far to be clear, if one considers for example that resistance of blood is positively correlated to hematocrit and whole blood viscosity when directly measured in blood, while at the whole body level these parameters are negatively correlated.

Clearly, the correlations between crude electric measurements at the whole body level and blood rheology remain hard to understand.

4. Analysis based on Hanai's mixture conductivity theory

Recent developments of the interpretation of BIA analysis based on Hanai's mixture conductivity theory allows a more interpretative analysis of the relationships between these electric measurements and body composition. Impedance can be analyzed in terms of resistance and resistivity of the whole body and even more, assuming some simplifications, resistance R and resistivity ρ of total body water (TBW), extracellular water (ECW) and intracellular water (ICW).

This approach may help to provide a link between these electric properties of the body and hemorheologic parameters. In this study we thus investigated relationships between blood rheology and these calculations of R and ρ in a sample of subjects in whom BIA was performed with a multifrequency bioelectrical impedancemeter

Body composition was assessed with a four terminal impedance plethismograph Dietosystem Human IM-Scan. The four electrode method minimizes contact impedance and skin-electrode interactions.

Measurements were made in fasting subjects after 15 min resting in a supine position. A low intensity (100 to 800 μA) current is introduced into the subject at various frequencies (1, 5, 10, 50 and 100 kHz). The measurement of the voltage drop allows the determination of total body impedance (Z) as a function of current frequency.

Since practical constraints and the occurrence of multiple dispersions prevent the use of a direct current (zero frequency) or very high frequency AC currents, the R values at the ideal measurement frequencies are predicted using a Cole–Cole plot [18] (negative reactance versus R plot), with R0 theoretically representing the R of the extracellular fluid (intracellular water) and R∞ representing the R of intra- and extracellular fluid (TBW). At zero (or low) frequency, the current does not penetrate the cell membrane, which acts as an insulator, and therefore the current passes through the extracellular fluid, which is responsible for the measured R of the body R_0. At infinite frequency (or very high frequency) the capacitor behaves as a perfect (or near perfect) capacitor, and therefore the total body R (R∞) reflects the combined of both intracellular and extracellular fluid.

In a second step of this analysis we used prediction equations based on the theory developed by Hanai [19] which describes the effect of a concentration (C) of nonconductive material on the apparent resistivity (ρ) of the surrounding conductive fluid, by introducing, as follows, an exponent $3/2$:

$$\rho=\rho_0/((1-C)^{3/2})$$

Resistivity ρ, resistance R and volume are related to each other according to the following relationship which includes an approximation of the human body shape through a dimensionless shape factor K_b

$$R= (K_b \rho H^2) / V_b$$

where V_b is the body volume, H the height, and ρ is the fluid resistivity. Van Loan et al. [20] obtained a value of 4.3 for K_b from statistical anatomical measurements in adults.

Then, with formulae developped on the basis of these assumptions, impedance can be analyzed in terms of resistance R and resistivity ρ of total body water (TBW), extracellular water (ECW) and intracellular water (ICW). A more complete presentation of the theoretical approach leading to all those calculations can be found in a recent review by Jaffrin [21]. At the end of the analysis total body bioimpedance data can be expressed in terms of Z, R, Xc, extracellular resistance Re , extracellular resistivity ρ_e , intracellular resistance Ri , intracellular resistivity ρ_i.

5. New findings with the approach of Hanai's mixture conductivity theory

Blood viscosity η was described by a classical robust model, Quemada's equation [22].

$$\eta = \eta_p(1-1/2\,\mathbf{k}\,\phi)^{-2}$$

where ϕ is hematocrit, η_p is plasma viscosity, and $\mathbf{k}(\dot{\gamma})$ is a shear-dependent parameter quantifying the contribution of erythrocyte rheological properties to whole blood viscosity. At high shear rate $\mathbf{k}(\gamma)$ is representative of red cell rigidity (ie, the lower $\mathbf{k}(\gamma)$ the higher is erythrocyte deformability), while at low shear rate $\mathbf{k}(\gamma)$ which tends to a maximum k_∞ that is proportional to the ability to form erythrocyte aggregates (red cell aggregability).

We found [23] a new prediction of Quemada's viscometric index of RBC rigidity "k" which was positively correlated to the resistance of ECW and even more if it was related to this volume : k = 0,005809 Re/VEC + 1,1784 (r=0,487; Bland-Alman : mean difference: 0,0124; range: -0,00481 - 0,00296). A new finding was

that RBC aggregability, that in the previous studies was not related to whole body impedance, despite its in vitro measurability with such measurements, was correlated to extracellular resistance and resistivity. The Myrenne index "M" was negatively correlated to the resistivity of the extracellular fluid ρ_e and is predicted by :$M = -27{,}4755\rho_e + 1121{,}57029$ (r=0.463; Bland-Alman : mean difference: 0,00194; range: -0,842 - 0,842). Furthermore, the SEFAM index "S_{10}" is correlated to the ρ_e and is predicted by $S_{10} = -59{,}38579 (\rho_e - 40) + 63{,}083$ (r=0.761; Bland-Alman : mean difference: 0,000722; range: -1,77 - 1,77).

6. Potential meaning of all these findings

Our previous studies on whole body impedance and hemorheology yielded the following correlations: whole body impedance (and resistance) are positively correlated to plasma viscosity and RBC rigidity. These correlations are logic, consistent with in vitro data. On the other hand the strongest correlation is a negative one between whole body impedance (and resistance) and both whole blood viscosity and hematocrit. The correlation with hematocrit explains the correlation with whole blood viscosity. It is unexpected and in discrepancy with in vitro data. With the use of Hanai's theory, Quemada's viscometric index of RBC rigidity "k" is positively correlated to the resistance of ECW, and RBC aggregability is correlated to extracellular resistance and resistivity. Therefore, there are two logic findings and two paradoxical ones. RBC rigidity and plasma viscosity, factors expected to impede blood flow, are associated with a higher electric resistivity and impedance. However, hematocrit and RBC aggregability are associated with a lower electric resistivity and impedance, ie the opposite of what is found in vitro. How can we explain this paradox? First of all, the relevance of hematocrit and RBC aggregability on blood flow at the whole body level is not the same as in vitro. Hematocrit seems to be associated with higher circulatory resistance in some local circulations (ie, brain circulation [24]) but not in others (ie, exercising muscle [25-26]). Similarly, RBC aggregation is a factor of decreased blood velocity in postcapillary venules [27] but has surely little or no relevance in high pressure high shear conditions [28]. Even more, it may decrease precapillary resistance in distal arterioles (Fahreus Lindqvist effect) [29] and thus facilitate blood flow, at least in some conditions.

These discrepancies between *in vitro* and *in vivo* effects of hematocrit and aggregation on blood flow may explain why these parameters are not positively correlated to resistivity and impedance. The fact that we find negative correlations rather than positive ones may be due to the effects of these parameters or of some others closely related to them (still to determine) on electric properties of flowing blood. We hypothesize that the positive correlation between resistivity at the whole body level and hematocrit may mostly reflect the fact that circulating RBCs are important electric charge carriers, while hematocrit in vivo has little or no negative influence on whole body arterial blood flow. Therefore, higher hematocrit would result in a facilitated circulation of electric charges in the arterial bloodstream, without reducing blood velocity, and thus would decrease whole body impedance.

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