Blood Electrical Impedance Closely Matches Whole Blood Viscosity as Parameter of Hemorheology and Inflammation

G.A.M. Pop[1*], W.J. Hop[3], L .Moraru[1], M. van der Jagt[4], J. Quak[6], D. Dekkers[5], Z. Chang[7], F.J. Gijsen[1], D.J. Duncker[2], C.J. Slager[1]

[1] Department of Cardiology, Thoraxcenter, Hemodynamics Laboratory EE2322, [2] Department of Cardiology, Experimental Cardiology, [3] Department of Biostatistics, [4] Department of Neurology, [5] Department of Biochemistry, [6] Laboratory of Hematology, Erasmus Medical Center Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands
[7] Department of Microelectronics, Technical University Delft

[*] Email: g.pop@cardio.umcn.nl
Fax: x31.24.3540537

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Abstract:
Red blood cell aggregation (RBCa) is a sensitive inflammation marker. RBCa determination from erythrocyte sedimentation rate, *ESR*, is used since long, but is unspecific unless corrected for hematocrit, *Ht*. Whole blood viscosity measurement at low shear rate is also sensitive to RBCa but is cumbersome to apply. To investigate whether electrical blood impedance, being sensitive to spatial red cell distribution, can be a good alternative to determine RBCa in low shear conditions. Blood was collected from 7 healthy volunteers. From each 16 different samples were prepared with 4 different *Ht*'s and with 4 different fibrinogen concentrations. Viscosity was measured at low shear rate (4.04 s^{-1}) with a rotational viscometer at 37˚C. Electrical blood impedance was measured during similar shear conditions and temperature in a specially designed cuvette. ESR was determined according to Westergren. A logarithmic increase of viscosity as well as of capacitance, C_m, is seen when fibrinogen rises and an exponential increase when *Ht* rises. However, *ESR* shows a logarithmic decrease with increasing *Ht* and an exponential increase when fibrinogen rises. The viscosity could be accurately described using an exponential model. Under similar low shear conditions and temperature in-vitro, either whole blood viscosity or electrical blood capacitance reflect red blood cell aggregation due to fibrinogen and *Ht* variation in a similar way.

Zusammenfassung:
Die Aggretation roter Blutkörperchen (RBCa) ist ein aufschlussreicher Test für Entzündungen. RBCa-Bestimmung aus der Sedimentationsrate der Erythrozyten, *ESR*, wird seit langem verwendet, aber ist unspezifisch so lange er nicht mit dem Hämatokritwert, *Ht*, korrigiert wird. Die Messung der Blutviskosität bei kleinen Scherraten ist ebenfalls RBCa-sensitiv jedoch schwierig in der Anwendung. Es wurde hier untersuchen, ob die Messung der elektrischen Impedanz, welche ebenfalls sensitiv auf die räumliche Verteilung der roten Blutkörperchen reagiert, eine gute Alternative zu Bestimmung der RBCa bei kleinen Scherraten ist. Blutproben von sieben gesunden Probandenwurden wurde so präperiert, dass 16 verschiedene Proben mit vier verschiedenen *Ht* und vier verschiedenen Fibrinogenkonzentrationen vorlagen. Die Scherviskositäten wurden bei kleinen Scherraten (4.04 s^{-1}) mit einem Rotationsrheometer bei 37˚C gemessen. Die elektrische Impedanz des Blutes wurde unter ähnlichen Scherraten und Temperaturen in einer speziell konzipierten Küvette gemessen, sowie die *ESR* nach dem Verfahren von Westergren bestimmt. Ein logarithmischer Anstieg der Viskosität als auch der Kapazität, C_m, wurde für einen ansteigenden Fibrinogenanteil, und ein exponentieller Anstieg für einen Hämatokritwertanstieg beobachtet. Die *ESR* zeigt jedoch eine logarithmische Abnahme mit ansteigendem Hämatokritwert and und einen exponentiellen Anstieg für einen Fibrinogenanstieg. Die Viskosität konnte mit Hilfe eines exponentiellen Modelles genau beschrieben werden. Unter vergleichbaren Bedingungen bei kleinen Scherraten und in-vitro-Temperaturen zeigen die Messungen der Blutviskosität und der elektrische Impedanzmessungen eine ähnliche Aggregation der roten Blutkörperchen auf Grund von Fibrinogen und *Ht*-Veränderung.

Résumé:
L'agrégation de cellules sanguines rouges (RBCa) est un indicateur très réceptif de l'inflammation. La détermination de la RBCa à partir de la vitesse de sédimentation de l'érythrocyte, ESR, est employée depuis longtemps, mais n'est pas spécifique si elle n'est pas corrigée en tenant compte de l'hématocrite, *Ht*. Les mesures de viscosité à faible vitesse de cisaillement de sang non traité sont elles aussi sensibles à la RBCa, mais sont délicates à appliquer. Nous avons cherché à savoir si la mesure de l'impédance électrique du sang, qui est sensible à la distribution spatiale en cellules rouges, peut être une bonne alternative à la détermination de la RBCa dans des conditions de faible cisaillement. Les échantillons de sang ont été collectés sur 7 volontaires sains. A partir de ces 7 échantillons, 16 échantillons différents ont été préparés avec 4 *Ht* différents et avec 4 concentrations en fibrinogène différentes. La viscosité a été mesurée à faible vitesse de cisaillement (4.04 s-1) à l'aide d'un visco-

occurs as has been described in earlier studies of viscometry [26] and photometry [27]. Both characteristics could be described very accurately by a newly developed formula, which was based on our own blood viscosity data at shear rate 4.04 sec^{-1} (Fig. 5). Extension of these findings to other shear rates may deliver a very accurate viscosity description based on *Ht* and fibrinogen content, which will be highly useful in the modeling of blood in computational fluid dynamics as applied in many patient studies.

In the last century the erythrocyte sedimentation rate, *ESR*, introduced by Fahraeus and Westergren in 1928 has been the most widely used clinical tool to measure the red cell aggregation. One of the important pitfalls of the *ESR* is its lack of specificity and sensitivity due to the influence of *Ht* [28] although a linear correction for *Ht* has increased its diagnostic value [29]. Our *ESR* data also show the influence of *Ht*, and from our data it appears that a non-linear correction should be made (Fig. 6). Indeed, whole blood viscosity at low shear is also strongly influenced by the *Ht* and this should be taken into account, when viscosity is used as inflammation marker. However, in contrast with ESR, viscosity is rightly positively correlated with *Ht* and therefore an increase in *Ht* cannot obscure an increase in fibrinogen.

Our experiments show a highly significant correlation between whole blood viscosity at low shear and the impedance parameter C_m measured in similar flow conditions (Fig. 7). In addition, the model developed for blood viscosity and its major variables *Ht* and fibrinogen could adequately describe the capacitance C_m as well. Although it is well known, that R_p may be used to estimate *Ht* [30] and therefore viscosity, the more specific fibrinogen dependency of C_m, as demonstrated in this study, may make the latter parameter more useful for determining inflammation marker proteins. Previously, the sensitivity of C_m to aggregation was described also in another set up, which however applied standstill of blood to reach an aggregation time up to 45 s [18]. In the current study we focused to measure C_m in a more physiological set up, applying flow reversal in the measuring set up each 2 seconds. Eventually, it is our goal to develop a catheter based impedance measuring set up, allowing recording of impedance changes as useful markers to predict changes in hemorheology. Using both impedance parameters, C_m and R_p it appeared possible to predict from these whether a clinically relevant variation occurred in *Ht* and/or fibrinogen at the same time. In the clinical setting hemorheology plays an important role in vascular hemodynamics and in the occurrence of thrombosis, in an acute as well as in a chronic situation. If hemorheology may be determined adequately by electrical impedance technique, on-line measurement might help to improve hemodynamic deterioration or to prevent thrombosis in patients and might help to evaluate medical therapy.

4.1 LIMITATIONS OF THE STUDY

A limitation of our study is that we were not able to measure the electrical parameters at exactly identical shear rate conditions as applied for whole blood viscosity determination. Therefore, instruments need to be developed to make this possible. Fibrinogen is not the only acute-phase protein that increases aggregation in a chronic inflammatory disease like atherosclerosis. C-reactive protein (CRP) and other acute-phase proteins have shown to have also effects on RBC aggregation [7]. But as RBC aggregation is the pivotal factor in this process and as C_m increases with the area of contacting cell membranes [31], the current results probably also reflect the effects when studying the addition of other acute-phase proteins.

CONCLUSION

Whole blood viscosity at low shear rate can be described accurately by a mathematical model, with hematocrit and fibrinogen as variables. This model adequately incorporates the non-linear effects of hematocrit and fibrinogen on viscosity. The combined electrical impedance parameters of blood, i.e. resistivity and capacitance, also accurately reflect changes in hematocrit and fibrinogen concentration and can thus be used to predict changes in whole blood viscosity. Consequently, the blood impedance measuring technique offers potential as detector of inflammation and is useful for estimation of changes in blood viscosity over time.

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