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On-Line Electrical Impedance Measurement for Monitoring Blood Viscosity during On-Pump Heart Surgery

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Key Words
Blood viscosity · Electrical impedance · On-pump heart surgery

Abstract
Background: The viscosity of blood (η) as well as its electrical impedance at 20 kHz at high shear rate depends on hematocrit, temperature, concentration of macromolecules and red cell deformability. The aim of our study was to investigate the relation between viscosity and electrical impedance in a heart-lung machine-like set-up, because during on-pump heart surgery considerable viscosity changes occur. ***Methods:*** Blood of 10 healthy volunteers was examined under temperature variation between 18.5 and 37 °C at four different levels of hemodilution. Blood viscosity was examined with a golden-standard technique, i.e. a Contraves LS 30 Couette viscometer, and the results were compared with measurements of the electrical resistivity (R) at 20 kHz by a specially designed device in series with the tubing system of a heart-lung machine. All measurements were performed at a shear rate of 87 s^{-1}. ***Results:*** Using stepwise multiparameter regression analysis (SPSS) a highly significant correlation was found (r^2 = 0.882) between viscosity (η) and resistivity (R). Adding the variables sodium ([Na^+]) and fibrinogen ([Fibr]) concentration the coefficient of correlation further improved to r^2 = 0.928 and the relation became: $\eta = -0.6844 + 0.038\,R + 0.038\,[Na^+] + 0.514\,[Fibr]$. All coefficients showed a statistical significance of p < 0.001. ***Conclusions:*** Electrical impedance measurement is feasible in a heart-lung machine-like set-up and allows accurate continuous on-line estimation of blood viscosity; it may offer an adequate way to record and control viscosity changes during on-pump heart surgery.

Introduction

Blood has non-Newtonian fluid dynamics characteristics, the most important of which is that its viscosity depends on shear rate [1, 2]. At intermediate (<50 s^{-1}) and especially at low (<1 s^{-1}) shear rate the viscosity significantly increases, whereas at high shear rate (>100 s^{-1}) blood behaves almost Newtonian and the viscosity only

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slightly drops with increasing shear rate [2]. The predominant cause of increasing viscosity when lowering shear rate is the occurrence of red blood cell (RBC) aggregation ('rouleaux formation') [3]. Normally in healthy persons, when the rising shear rate is $>100\ s^{-1}$, all RBC aggregates are dispersed [1] and RBC deformability becomes an important factor determining blood viscosity [3]. Other important determinants of blood viscosity are the hematocrit (number of cell-cell interactions), the temperature and the concentration of macromolecules (cell-protein interactions) in the suspending medium, influencing the intensity of red cell-cell interactions [1–4].

Interestingly, the electrical impedance of blood shows a similar dependency of the most important viscosity determining parameters [5, 6]. The electrical resistivity of whole blood, measured at low frequency (20 kHz), is highly dependent on hematocrit, because the isolating membranes of the RBCs are not conducting below 100 kHz [7, 8]. Similar to blood viscosity, the electrical impedance of blood will increase at low shear rate because of RBC aggregation (rouleaux formation) [5], which diminishes the accessible conducting plasma volume. At higher shear rates the electrical impedance, measured in parallel with the flow streamlines, is dependent on the deformability of the RBC [9]. Similar to viscosity, the electrical resistivity (at 20 kHz) of blood will reach an almost constant plateau for shear rates $>100\ s^{-1}$ and the level of the plateau is dependent of the red cell deformability [9]. Also similar to viscosity is that both a decrease of temperature as well as an increase of macromolecules (especially fibrinogen) in the medium will increase the electrical impedance of blood [5, 10]. Electrical impedance measurement has been used for determining hematocrit on-line [11] but variation in temperature and concentration of macromolecules (like fibrinogen) make blood resistivity more correlated with whole blood viscosity than with hematocrit. For all these reasons, measuring blood resistivity might provide, under certain circumstances, an easier alternative for the estimation of blood viscosity.

The aim of our study was to compare in a direct way blood viscosity determined by a Couette viscometer with electrical resistivity of blood determined by the four electrodes measuring technique at low frequency (20 kHz). Measuring conditions were adapted to the situation of on-pump open-chest heart surgery as in this condition considerable viscosity changes occur [12, 13]; monitoring these viscosity changes by an on-line electrical resistivity measurement device might be of clinical benefit.

Material and Methods

Population and Experimental Set-Up

After informed consent had been obtained from 10 healthy male volunteers with a mean age of 33 (range 25–50) years, 300 ml blood was taken from the antecubital vein. Two volunteers were smokers. No history of infection was present in the weeks before blood donation. Blood was heparinized (40 U/ml) and placed in a heart-lung machine-like set-up (fig. 1). This set-up consisted of a centrifugal pump, a reservoir for pediatric use and a Tygon® tubing system with restricted length. The temperature was controlled by a Heater-Cooler® (Stöckert, Munich, Germany) and flow was measured instantaneously by an electromagnetic flow probe (H6xl®, Transonic Systems Inc., Ithaca, N.Y., USA).

Viscosity Measurement

Blood viscosity was determined with the Contraves LS 30 Couette viscometer (Zürich, Switzerland), allowing measurements at different temperatures. Blood viscosity was determined at the highest shear rate ($87\ s^{-1}$) that could be reliably applied. A corresponding shear rate at the location of the electrical resistivity measurement within the heart-lung machine was obtained by selecting a mean flow of 442 cm^3/min calculated according to the formula: shear rate = 4 × mean velocity/radius [2].

Impedance Measurement

The impedance measurement system consisted of four stainless steel electrode rings mounted in-line with the wall (fig. 2); the two outer current delivery electrodes were positioned at equal distances from the two inner measurement electrodes. The electrodes were connected with an impedance-measuring instrument (Goovaerts Instruments, Kortenhoef, The Netherlands) [14]. Between the current electrodes, an alternating (20-kHz) current of $<100\ \mu A_{rms}$ was applied and between the measurement electrodes the voltage was recorded. Blood cells are not altered at these low currents [15]. Calibration of the device was performed with physiologic 0.9% NaCl solution in a special impedance-measuring instrument (CD Leycom, Zoetermeer, The Netherlands). Using the obtained calibration constant, the specific resistivity of blood in the device was calculated.

Physiological Variables

The condition of on-pump heart surgery was simulated by inducing hypothermia until 18.5 °C and increasing the temperature subsequently to 25, 32 and 37 °C. Temperature stability could be maintained within a reading of 0.1 °C. The other important parameter of hemodilution was varied by adding a plasma expander (Gelofusine®, B. Braun, Melsungen, Germany). Therefore, baseline hematocrit and three lower hematocrits (until 22%) were obtained. For each hematocrit value, measurements were performed at four different temperatures.

For each hematocrit sample, sodium (Na^+), hematocrit (Hct) and pH were measured in a GEM Premier 3000 (Instrumentation Laboratory, Lexington, Mass., USA) at the beginning (18.5 °C) and at the end (37 °C) of the viscosity measurements. The interval between measurements at each dilution and at the four different temperatures (T) was <20 min.

Statistics

Unless otherwise stated, all results are expressed as mean ± SD. The paired Student's t test was used to compare differences between

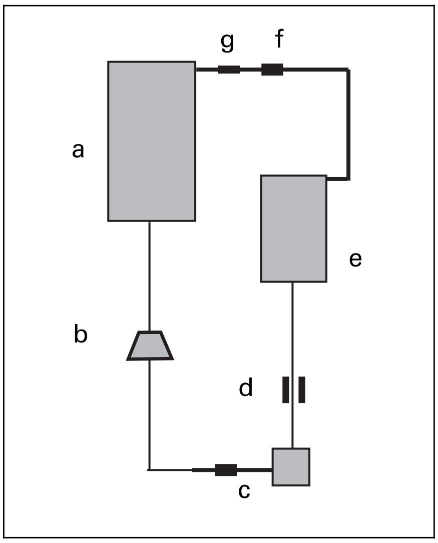

Fig. 1. Schematic diagram of the 'heart-lung machine'-like set-up. **a** Venous reservoir, Polystan Safe Micro, Copenhagen, Denmark. **b** Centrifugal pump, Biomedicus BP-50 Medtronic, Eden-Prairie, Minn., USA. **c** Heater-Cooler, Stöckert, Munich, Germany. **d** Flow probe H6xl, Transonic Systems, Inc., Ithaca, N.Y., USA. **e** Heat-exchanger, Polystan Safe Micro, Copenhagen, Denmark. **f** Impedance device (see fig. 2) **g** Temperature probe, Mallinckrodt Medical, St. Louis, Mo., USA.

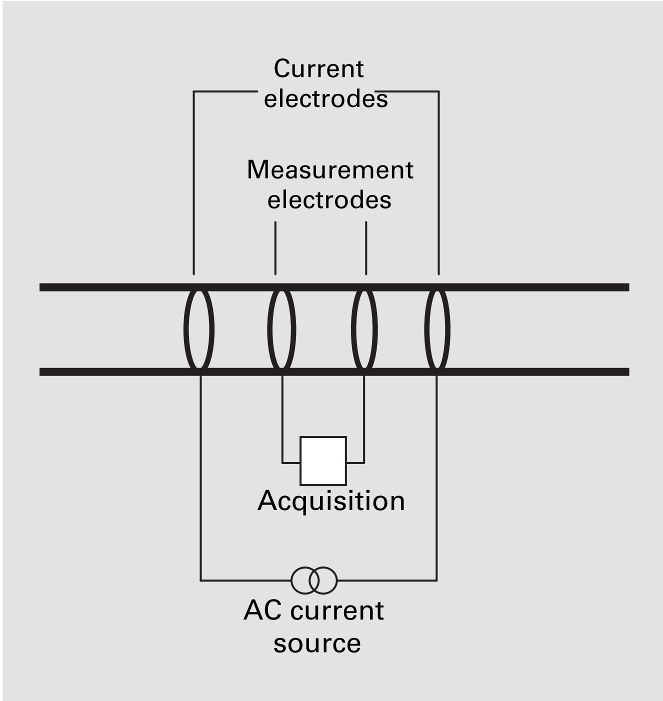

Fig. 2. Blood impedance-measuring device for heart-lung machine.

pH, Na^+ and Hct at 18.5 and 37 °C. Multiple stepwise regression was applied to relate viscosity and resistivity to Hct, T, Na^+, Fibr and pH. Similarly, a regression model was developed to predict viscosity from resistivity. All statistics were calculated using the software package SPSS (version 9.0 for Windows, Microsoft). A p value of <0.05 was considered to be statistically significant.

Results

The intake Hct varied from 37 to 51% (44.7 (SD 4.1)). All individuals had normal levels of fibrinogen, varying from 1.98 to 2.85 g/l with a mean of 2.33 (SD 0.27).

Relating blood viscosity (η) in a multiparameter model with stepwise regression analysis to the variables Hct and T yielded a correlation coefficient (r^2) of 0.888 for a logarithmic relation. Adding pH, r^2 increased to 0.903 and after adding Na^+ r^2 increased to 0.908. Finally, adding fibrinogen raised r^2 minimally to 0.911. Considering a rise in r^2 <0.005 as clinically insignificant, the subsequent formula was obtained:

$$\ln(\eta) = -5.129 + 0.0276\,\mathrm{Hct} - 0.0223\,T + 0.0026\,[Na^+] + 0.801\,\mathrm{pH} \quad (1)$$

where η = blood viscosity (mPa·s), Hct = hematocrit (%), T = temperature (°C), $[Na^+]$ = Na^+ concentration (mmol/l), and pH = logarithmic acid-base balance. All coefficients were highly significant ($p < 0.001$).

Relating the specific electrical resistivity R to the variables Hct and T yielded for a logarithmic relation an r^2 = 0.957. Adding Na^+ raised r^2 to 0.974. Adding pH and fibrinogen raised r^2 minimally to respectively 0.976 and 0.977 ($p < 0.001$ for all coefficients). Considering again a rise of r^2 <0.005 as clinically insignificant, the subsequent formula was obtained:

$$\ln(R) = 5.157 + 0.0252\,\mathrm{Hct} - 0.0207\,T - 0.0039\,[Na^+] \quad (2)$$

where R = specific resistivity (ohm·cm), Hct = hematocrit (%), T = temperature (°C), and $[Na^+]$ = Na^+ concentration (mmol/l).

Relating blood viscosity to the specific electrical resistivity showed r^2 = 0.882. An overview of the data is depicted in figure 3. Adding $[Na^+]$ raised r^2 to 0.921 and adding fibrinogen concentration raised r^2 to 0.928. There was a clinically non-significant further increase to r^2 = 0.930, when the initial pH was entered ($p < 0.0001$ for all coefficients). Therefore, the relation between viscosity

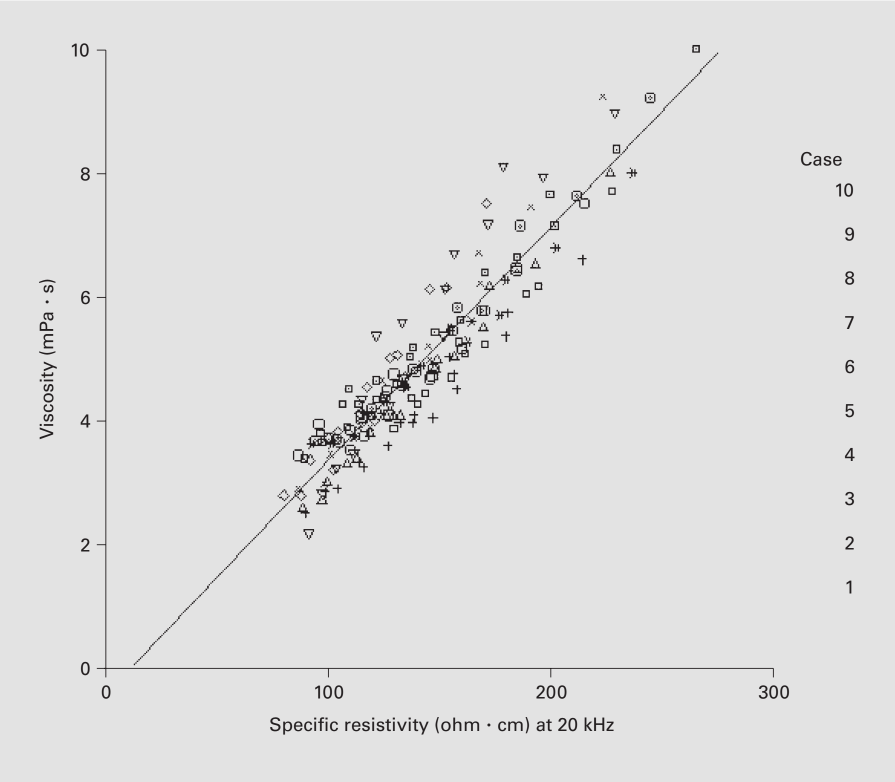

Fig. 3. Relation between measured viscosity and measured resistivity of blood at 20 kHz.

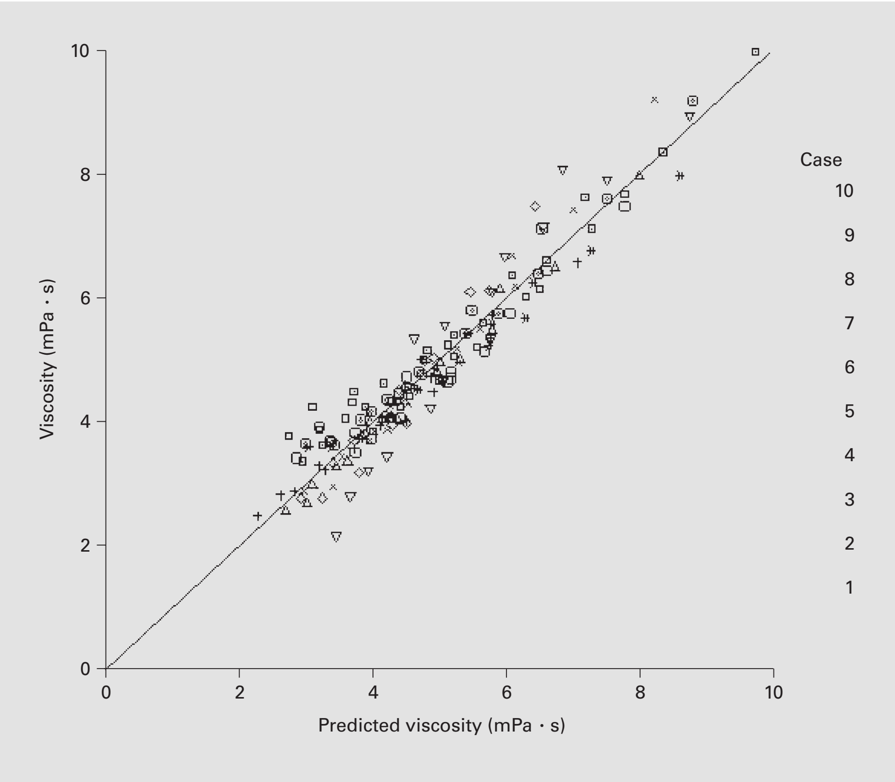

Fig. 4. Measured viscosity plotted against viscosity as predicted by equation 3.

and the specific electrical resistivity adding the variables [Na^+] and [Fibr] for all Hcts and temperatures became:

$$\eta = -0.6844 + 0.038\,R + 0.038\,[Na^+] + 0.514\,[Fibr] \quad (3)$$

where η = blood viscosity (mPa·s), R = specific resistivity measured at 20 kHz in (ohm·cm), [Na^+] = Na^+ concentration (mmol/l), and [Fibr] = fibrinogen concentration (g/l).

The measured viscosity is plotted against the predicted value of blood viscosity in figure 4.

Comment

In this experimental study we examined a wide range of changes of human blood viscosity as a function of hematocrit and temperature in a set-up which closely resembles the situation of on-pump open-chest heart surgery and compared these with variations in blood resistivity. All measurements were done at a comparable high shear rate of 87 s^{-1} under which blood of healthy persons reaches Newtonian [1, 2] behavior and both viscosity and electrical resistivity asymptotically reach a plateau [6,9]. A remarkably high correlation between viscosity and electrical resistivity was found.

Parameters determining resistivity as well as viscosity of blood showed to have almost the same effect except for sodium. The physiologic variation of sodium in whole blood ranges from 135 to 145 mmol/l, which perfectly fits with our measurement results (138 ± 7.4 mmol/l). From the regression analysis it appears that an increase of 10 mmol/l Na^+ results in a 3.9% decrease of electrical resistivity and a 3.1% increase of blood viscosity. The influence of the sodium level on blood resistivity is almost conform to the data predicted by Fuller [8] based on his plasma simulation model. A reduced deformability [16] and a reduced surface charge of the RBCs [17] may explain the influence of Na^+ on viscosity. Consequently, when the electrical resistivity is used as a parameter for blood viscosity at high shear, accuracy is improved by correcting for sodium level. However, normally Na^+ levels will change with <10 mmol/l during heart surgery, because isotonic plasma expanders are used for hemodilution.

The influence of fibrinogen on blood viscosity and resistivity has been reported before [10, 18]. The influence of fibrinogen is particularly predominant at low shear rate. However, because the levels of fibrinogen in the healthy volunteers were low and similar, only a modest effect of fibrinogen was observed in this study. Nevertheless, the effect of fibrinogen on resistivity was statistically significant, illustrating the sensitivity of our measurements.

Considering the results obtained in this study, on-line determination of electrical resistivity of blood may be a valuable measurement method during on-pump heart surgery as a substitute of the more cumbersome repeated blood viscosity determination. Blood viscosity may be an important parameter to be evaluated [12, 13, 19, 20]; measuring resistivity may be helpful to select optimal hemodilution [21] in order to counteract the negative effects of hyperviscosity. Several studies have demonstrated the presence of reduced RBC deformability after on-pump heart surgery and hypothermia has been shown as one of the causes [12]. Previous impedance studies have shown that reducing RBC deformability by hardening are reflected in increased electrical resistivity at 20 kHz [9, 22]. The reduced RBC deformability may adversely affect capillary recruitment preventing adequate delivery of oxygen to tissue [23, 24]. Viscosity [2] as well as electrical impedance of blood [9] at high shear rate, as present in the tubes of the heart-lung machine, are dependent of RBC deformability. Clinical studies during on-pump heart surgery with use of our electrical impedance technique are warranted to investigate whether it reflects adequately blood viscosity level on-line and whether post-operative cerebral and renal dysfunction [25–27] might be partially due to hyperviscosity.

Limitations of the Study

The excellent squared correlation of electrical resistivity with hematocrit, temperature and Na^+ concentration (equation 2) indicates that the electrical resistivity of blood at a certain shear rate can be predicted accurately from these variables. In other words, the resistivity measurement shows a low signal-to-noise ratio, as the unexplained $(1 - r^2) \cdot 100\%$ fraction of the relation, i.e. 2.6%, is very low [28]. In contrast, the correlation between blood viscosity and these three variables (equation 1) shows a somewhat smaller correlation, and the unexplained relative fraction is 9.2%. It is possible that we missed a yet unknown variable, which might influence viscosity and not the electrical resistance. However, another more likely explanation might be that the viscosity measurements at lower levels show more noise. For rotational viscometers in general, the accuracy of measurements decreases for less viscous liquids and at highest shear rates [29]. Indeed, our data also show a decreasing correlation between viscosity and resistivity at the lower viscosity levels.

We measured blood viscosity at shear rate 87 s^{-1}, because this was the maximal shear in the Contraves LS

30. Using blood from healthy volunteers, we could expect that all RBC aggregates are dispersed at this shear rate [1, 2]. During a real coronary bypass surgery with a mean perfusion flow of 5 l/min, shear rates are >400 s^{-1}. Then, also blood cells from patients will be fully dispersed, especially as hematocrit is normally lowered by hemodilution before connecting the heart-lung pump; a lower hematocrit [2]. Nevertheless, future investigations have to elucidate the influence of a raised fibrinogen concentration or other proteins on the correlation between viscosity and electrical resistance at high shear rate in a patient population.

A blood oxygenator was not added in our experimental set-up because this would require too much donation of blood. However, in almost all blood samples measured with the GEM Premier 3000 (Instrumentation Laboratory) the oxygen saturation remained between 95 and 100% during the entire experiment. Furthermore, Kameneva et al. [12] did not consider the oxygenator as a specific factor of mechanical stress in their study of decreased RBC deformability due to cardiopulmonary bypass. In our experimental set-up we focused on the major influence of hypothermia and hemodilution on blood viscosity and resistivity.

In our study the relation between electrical resistivity and blood viscosity is measured at high shear rate only. As blood has non-Newtonian characteristics, the viscosity will rise steeply at low shear rate, especially because of aggregation [1, 2]. Studies of electrical impedance, at frequencies in the range from 20 to 1,200 kHz in blood and at low shear rate, suggest that a relation exists between blood capacitance and the aggregation tendency between RBCs [5]. This correlation between electrical impedance and viscosity at low shear rate has to be further defined.

Finally, in our study the described method to determine blood viscosity can be used only during the on-pump time; however, during this time greatest viscosity changes are present, especially if more hypothermia is being applied.

Conclusion

Electrical resistivity measured on-line at relatively low frequency (20 kHz) in a heart-lung machine-like set-up has a good correlation with blood viscosity at high shear rate. This shows that estimation of blood viscosity by a well-defined impedance measurement is feasible.

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