On-line blood viscosity monitoring in vivo with a central venous catheter, using electrical impedance technique

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Abstract
Blood viscosity is an important determinant of microvascular hemodynamics and also reflects systemic inflammation. Viscosity of blood strongly depends on the shear rate and can be characterized by a two parameter power-law model. Other major determinants of blood viscosity are hematocrit, level of inflammatory proteins and temperature. In-vitro studies have shown that these major parameters are related to the electrical impedance of blood. A special central venous catheter was developed to measure electrical impedance of blood in-vivo in the right atrium. Considering that blood viscosity plays an important role in cerebral blood flow, we investigated the feasibility to monitor blood viscosity by electrical bioimpedance in 10 patients during the first 3 days after successful resuscitation from a cardiac arrest. The blood viscosity–shear rate relationship was obtained from arterial blood samples analyzed using a standard viscosity meter. Non-linear regression analysis resulted in the following equation to estimate in-vivo blood viscosity (Viscosityimp) from plasma resistance (Rp), intracellular resistance (Rl) and blood temperature (T) as obtained from right atrium impedance measurements:

Viscosityimp = (−15.574 + 15.576RlRTC0.138δRi+0.290Ri) R Ti C0.31 24 3540537.

This model explains 89.2% (R² = .892) of the blood viscosity–shear rate relationship. The explained variance was similar for the non-linear regression model estimating blood viscosity from its major determinants hematocrit and the level of fibrinogen and C-reactive protein (R² = .884). Bland–Altman analysis showed a bias between the in-vitro viscosity measurement and the in-vivo impedance model of .04 mPa s at a shear rate of 5.5 s⁻¹ with limits of agreement between −1.69 mPa s and 1.78 mPa s. In conclusion, this study demonstrates the proof of principle to monitor blood viscosity continuously in the human right atrium by a dedicated central venous catheter equipped with an impedance measuring device. No safety problems occurred and there was good agreement with in-vitro measurements of blood viscosity.

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1. Introduction

Blood is a concentrated suspension of blood cells in plasma and it exhibits a range of non-Newtonian properties (Gijzen et al., 1999; Chien et al., 1987). These properties are mainly due to deformation and aggregation of red blood cells, with the consequence that the viscosity of blood is not constant but is strongly dependent on shear rate. The widely used two parameter power-law model is a generalized Newtonian model that can be used to describe the shear rate dependence of blood viscosity (Gijzen et al., 1999).

At a particular shear rate the resistance (R) of blood flow is determined by a vascular and a viscous component such as expressed in the Hagen–Poiseuille equation: \( R = \frac{8\eta l}{\pi r^4} \), in which \( r \) is vessel radius, \( l \) is vessel length and \( \eta \) is blood viscosity. The shear rate dependency of blood viscosity has a great impact on areas within the circulation that exhibit a low shear rate such as the microcirculation. With increasing viscosity, plugging of the capillary bed might occur followed by arterio-venous shunting and diminished tissue perfusion (Chien et al., 1987). Blood viscosity increases during inflammation due to aggregating forces...
of acute phase proteins on blood cells (Lowe et al., 1981; Koenig and Ernst, 1992; Woodward et al., 1999). Inflammation is one of the major responses of the body to internal and external stimuli. Numerous studies in the last decades have demonstrated that atherosclerosis is also a chronic inflammatory disorder (Ross, 1999; Libby and Ridker 1999; Libby et al., 2002). Increased blood viscosity has been shown to predict worse cardiovascular short-term and long-term outcome (Ridker et al., 2000).

Since the eighteenth century electrical impedance measurements have been used to examine the bulk electrical properties of tissues (Fricke and Morse, 1925; Pribush et al., 1999; Pribush et al., 2000). In 1925, Fricke described the electrical characteristics of whole blood in a three-element model, in which $R_p$ (plasma resistance) is placed in parallel with $C_m$ (membrane capacitance), which is in series with $R_i$ (total intracellular resistance). Several studies with this model confirmed the close relationship between hematocrit ($Ht$) and the electrical resistivity at low frequencies (20–100 kHz; Hill and Thompson, 1975; Fricke, 1953). Other studies have shown the relationship of blood flow and the fibrinogen level with the electrical characteristics of blood at higher frequencies (100–1500 kHz, Zhao and Jacobson, 1997; Beving et al., 1994). Considering that hematocrit, flow and fibrinogen are important determinants of blood viscosity, our group demonstrated in 2003 that blood electrical impedance closely matches whole blood viscosity as a parameter of hematology and inflammation (Pop et al., 2003). This in-vitro study was followed by an in-vivo study in animals, in which catheter-based impedance measurements in the right atrium were shown to be feasible and allowed continuous measurement of hematocrit and blood viscosity (Pop et al., 2004).

Since viscosity is a major determinant of blood flow, continuous in-vivo measurement may yield continuous in-vivo information on determinants of flow and inflammation and may guide therapy. The present pilot-study in humans was undertaken to investigate the feasibility of on-line measurement of blood viscosity using a central venous impedance catheter. We investigated this in patients during the first 3 days after successful resuscitation from out-of-hospital cardiac arrest. In these patients, the post-resuscitation period is characterized by changes in macrovascular and microvascular cerebral blood flow (Holzer et al., 2005; Ristagno et al., 2008). In addition, the ischemia–reperfusion injury in these patients is associated with a systemic inflammatory response (Adrie et al., 2004). Whole blood viscosity is a major determinant of macro- and microvascular flow and at the same time viscosity is dynamically influenced by inflammation; therefore, continuous monitoring of blood viscosity may be clinically relevant in these patients. The aims of the study were (I) to measure the electrical impedance of blood in the right atrium of the heart; (II) to establish a mathematical equation to determine blood viscosity from on-line electrical impedance measurements in the right atrium and blood temperature by non-linear regression of the in-vitro blood viscosity measurements as obtained with a Contraves LS 300; (III) using the same non-linear regression analysis to establish a mathematical equation to estimate blood viscosity from the major determinants of blood viscosity: hematocrit and the acute phase proteins fibrinogen and CRP in addition to blood temperature; and (IV) to compare the in-vitro blood viscosity measurements with the Contraves and the two models of indirect viscosity estimation by Bland–Altman analysis.

2. Methods

2.1. Study population

We performed a prospective observational study in 10 comatose patients successfully resuscitated from an out-of-hospital cardiac arrest treated with mild therapeutic hypothermia. The local Institutional Review Board approved the protocol and written informed consent was obtained from the nearest relative. All patients of 18 years or older were eligible for the study if they were comatose (Glasgow Coma Scale score < 6) after return of spontaneous circulation. Patients were excluded if they were pregnant, received thrombolytic therapy, had refractory cardiogenic shock, or had a life expectancy of < 24 h.

2.2. Patient management

All patients were admitted to the ICU of our tertiary care university hospital in Nijmegen, The Netherlands. If necessary, a coronary angiogram and a percutaneous coronary intervention were performed before admission to the ICU. According to our standard protocol, patients were cooled to 32–34 °C by rapid infusion of 30 ml/kg body weight of cold Ringer’s lactate at 4 °C followed by external cooling using two water-circulating blankets (Blanketroll II Cincinatti Subzero, The Surgical Company, Amersfoort, The Netherlands). Temperature was measured continuously with a rectal temperature probe (YSI Incorporated 401, van de Putte Medical, Nieuwegein, The Netherlands) and maintained at 32–34 °C for 24 h, followed by passive rewarming to normothermia (defined as 36.5 °C). All patients were intubated and mechanically ventilated aiming at an arterial oxygen partial pressure (PaO2) > 75 mmHg and arterial carbon dioxide pressure (PaCO2) between 34 and 42 mmHg. Alpha-stat was used for pH maintenance. The radial or femoral artery was cannulated for monitoring of blood pressure; the intra-arterial line was also used for periodic sampling of blood for measurement of hematocrit, fibrinogen, CRP and viscosity. The HemoCard Vision catheter was introduced into the right atrium via the right internal jugular vein using a Seldinger technique (Fig. S1, Supplement on-line). A fourth lumen is used for measurement of hematocrit, fibrinogen, CRP and viscosity. The HemoCard Vision catheter has a heparin-based hydrophilic coating to enhance catheter patency.

2.3. In-vivo right atrium impedance measurement

The HemoCard Vision catheter is a dedicated 8.25 French, 30 cm, 3-lumen central venous catheter of polyurethane of 30 cm length (Fig. S2, Supplement on-line). A fourth lumen is used for co-axial insulated cables, which are connected to four different electrodes at the tip. In order to satisfy the electro-magnetic emission requirements of the IEC60601 norm, the actively-guarded cables are enveloped by a second grounded shield. An excitation current of 10 $\mu$Ams is applied to the outer excitation electrodes and the whole-blood complex–impedance is measured between the inner sensing electrodes by applying a sinusoidal excitation signal at four frequencies: 100 kHz, 200 kHz, 625 kHz and 1.25 MHz. The frequencies are applied each for 10 ms at a time. An intracavitary ECG signal is also separately extracted from the two inner electrodes. Furthermore, a thermistor incorporated at the catheter’s tip allows central blood temperature measurement. Impedance, temperature and ECG signals are extracted at 10 min intervals for 18 s.

The ECG, blood complex impedance and temperature readings are processed by an electronic interface (Fig. S2, Supplement online) and sent wirelessly to an external monitor. The entire catheter has a heparin-based hydrophilic coating to enhance hemocompatibility and to prevent the formation of a biofilm or thrombus. The tip of the catheter is introduced up to the middle...
of the right atrium using the intracavitary ECG signal and the impedance signal as monitors to prevent erroneous positioning of the catheter. Appearance of the QRS-signal means that the tip is too deep near the right ventricle and the lower the impedance signal the better the tip is located in the middle of the blood volume inside the right atrium.

2.4. Data collection

Blood was sampled at 0, 3, 6, 12, 24, 36, 48 and 72 h after insertion of the impedance catheter. Standard laboratory techniques were used to measure Ht, fibrinogen, and C-reactive protein. Blood viscosity was determined at shear rates from .2 s\(^{-1}\) to 50 s\(^{-1}\) and measured in-vitro with a Contraves LS 300 (proRheo, Germany). Electrical impedance was measured automatically every 10 min. Only the impedance data obtained at the time of blood sampling were used for comparison. Occasionally data were missing due to the inability to obtain blood (5%) and to technical problems met with either laboratory (8%) or impedance-measurement equipment (6%). To allow unbiased comparison between the two methods of viscosity estimation, only the complete data sets were used for comparison. From the maximum of 80 data sets that could have been obtained a total of 15 were missing. The following list shows the time and the number of complete data sets obtained between brackets, \(t=0\) (10), \(t=3\) (8), \(t=6\) (9), \(t=12\) (8), \(t=24\) (7), \(t=36\) (8), \(t=48\) (8) and \(t=72\) (7).

2.5. Impedance measurement and data analysis

To rule out random variation and variation resulting from volume and shear rate changes in the right atrium of the heart during the cardiac cycle, the mean values of current and voltage data acquired during the 18 s measuring period were calculated and used for further analysis.

The electrical impedance \((Z)\) measured in blood was modeled by a resistor \((R_p)\) in parallel with a resistor \((R_i)\) and capacitor \((C_m)\) in series according to the original description by Fricke and Morse in 1925 (Fricke and Morse, 1925). Applying this model the impedance \(Z\) can be written as

\[
Z = \frac{R_p(R_p+1/j\omega C_m)}{R_p+R_i+1/j\omega C_m}
\]

in which \(j = \sqrt{-1}, \omega = 2\pi f\) and \(f=\)frequency.

The values of this 3-element model were found by minimizing the function

\[
M = \sum_{n=1}^{3} (V_n-[I_nZ_n])^2
\]

The indices \(n=1, 2\) and 3 represent the frequencies 100 kHz, 625 kHz and 1250 kHz respectively in voltage \((V_n)\), Current \((I_n)\) and impedance \((Z_n)\).

To find the minimum of the multi-variable function \(M\) an iterative algorithm, known as unconstrained non-linear optimization, was used. The search started at an initial estimate that was calculated as follows

At the frequency \((f_1=100\ km\) the impedance of \(R_i\) in series with \(C_m\) is relatively high and the electrical current flows mainly through \(R_p\). Using Ohm’s law, \(R_i\) can be estimated as \(V_1/I_1\). At the highest frequency \((f_3=1250\ km\) the impedance of \(R_i\) in series with \(C_m\) is at its lowest value and, the current flowing through \(R_i\) and \(C_m\) reaches its maximum value compared with the currents at 100 kHz and 625 kHz respectively. As the current through \(R_p\) still obeys Ohm’s law, the current through \(R_i\) and \(C_m\) can be estimated as \(I_i = I_2-V_2/R_p\). Taking as a starting point in our calculations a phase angle of 45° between the real \((R_i)\) and the imaginary part \((1/j\omega C_m)\), the initial value \(R_i\) can be calculated as \(V_2/I_2(2)\) and \(C_m = \omega V_2/V_3\). The minimum value of the function \(M\) converges to a value of less than \(10^{-10}\) for all impedance measurements, indicating that the model assumptions are met. All calculations were performed using Matlab R2011b (The MathWorks, Inc. Natick, MA, USA).

2.6. Shear rate dependent blood viscosity model

Human blood can be characterized as a non-Newtonian fluid (Chien et al., 1987) and its viscosity cannot be described by a single number. The power-law model is a generalized Newtonian model used to model the behavior of blood (Gjisen et al., 1999):

\[
\eta = A \text{(shear rate)}^B
\]

The two parameters in this model, \(A\) and \(B\), describe the dependency of blood viscosity on shear rate. On a limited shear rate range, blood viscosities can well be described by this model.

Shear rates higher than 50 s\(^{-1}\) will approach a horizontal asymptote and shear rates lower than .2 s\(^{-1}\) will approach a vertical asymptote. Therefore, with larger intervals, a model using more parameters such as the Carreau-Yasuda model (Gjisen et al., 1999), is needed to accurately describe the viscosity of blood. In this study the viscosity of all blood samples were analyzed on a clinically relevant shear rate interval limited between .2 s\(^{-1}\) and 50 s\(^{-1}\). To characterize the viscosity of a blood sample, the values \(A\) and \(B\) from the power function fit were used.

3. Statistical analysis

Data are presented as mean and standard deviation. The paired Student-T test is applied to compare mean differences between longitudinally obtained data with data obtained at the start of data collection (time—0).

We used non-linear regression analysis to find the mathematical model parameters to estimate blood viscosity. Non-linear regression can estimate models with arbitrary relationships between independent and dependent variables. This was accomplished using iterative estimation algorithms. Appropriate initial (starting) values are necessary, in order to converge to an absolute minimum rather than a local minimum.

As described in the introduction, evidence exists that blood viscosity is related with the impedance parameters \(R_p\), \(C_m\) and \(R_i\). It was assumed that the viscosity values \(A\) and \(B\) from the 65 blood samples collected in this study can be described by two separate multiple linear functions. Necessarily, not all mentioned independent variables will significantly contribute to the dependent viscosity variables \(A\) or \(B\), as obtained in this study. Therefore, stepwise regression analysis was applied to exclude the independent variables and their interaction terms that are not statistically significant related to the dependent viscosity variables \(A\) and \(B\) respectively. The non-linear regression procedure was started using the parameters found to describe \(A\) and \(B\) as initial values. Notice that in this procedure the dependent variable was the viscosity expressed in mPa.s as obtained with the calibrated Contraves LS 300 and shear rate was added to the dependent list. R-squared as a measure of explained variance is used to describe the goodness of fit.

The same procedure was repeated using temperature, hematocrit, and the inflammatory proteins fibrinogen and C-reactive protein as independent variables. The Bland–Altman method (Bland and Altman, 1986) was applied to compare the "indirect" model derived viscosity estimates at a shear rate of 5.5 s\(^{-1}\) and the actual "direct" viscosity as measured with the Contraves LS 300.
All statistical analysis was performed using the SPSS package (SPSS Inc., IL, USA) release 16.0. The level of statistical significance was set at .05.

4. Results

4.1. Population

We studied 10 comatose patients successfully resuscitated from an out-of-hospital cardiac arrest. The median age was 68.0 (53.5–74.5) years, 8 of 10 patients were male. A coronary angiogram and a percutaneous coronary intervention was performed in 6 patients before admission to the ICU. Median temperature at the start of the study was 33.4 (33.0–35.5) °C and was maintained between 32 and 34 °C for 24 h. All patients were passively rewarmed after 24 h from 34.2 (32.8–34.9) °C at 24 h to 37.4 (37.2–37.7) °C at 72 h after admission (p < .001). Three patients died in the ICU, all because of severe postanoxic brain damage.

4.2. General performance and safety of the HemoCard vision system

Catheter-related complications did not occur either during introduction of the HemoCard Vision catheter or during the following 72 study hours. Introduction of the catheter and positioning the tip of the catheter in the middle of the right atrium by using the intracavitary ECG signal took 20–25 min. Atrial arrhythmias were not seen.

4.3. Absolute changes in time of blood viscosity, hematocrit, fibrinogen, CRP and impedance ($R_p$, $R_i$ and $C_m$).

We measured the electrical impedance of blood in the right atrium at different points in time for 72 h after admission. In Table 1 all relevant values related to the viscosity measurements at the start of the study (time = 0) are shown. Mean values are taken from all absolute changes in each patient paired to the value at $T = 0$. These mean values of absolute changes in blood viscosity, hematocrit, fibrinogen and CRP are depicted in Fig. 2. The absolute changes of the electrical impedance values ($R_p$, $R_i$ and $C_m$) are depicted in Fig. S4 (Supplement on-line).

Blood viscosity at SR 5.5 s$^{-1}$ was the highest during the initial hours and decreased significantly only after 36 h. Hematocrit showed a similar change in time as compared to blood viscosity;

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Std. error</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p_1$</td>
<td>−15.576</td>
<td>.663</td>
<td>−16.875 to −14.273</td>
</tr>
<tr>
<td>$p_2$</td>
<td>15.576</td>
<td>.321</td>
<td>14.947 to 16.205</td>
</tr>
<tr>
<td>$p_3$</td>
<td>−138.13</td>
<td>.065</td>
<td>−150 to −125</td>
</tr>
<tr>
<td>$p_4$</td>
<td>−290.23</td>
<td>.037</td>
<td>−363 to −216</td>
</tr>
</tbody>
</table>

Fig. 1. Absolute changes of blood viscosity (measured with the Contraves LS 300 at shear rate 5.5 s$^{-1}$), hematocrit, fibrinogen and CRP (C-reactive protein) compared to their levels at starting time (Time = 0). Bars denote 95% confidence interval (CI), and dots denote the mean.

Table 1

<table>
<thead>
<tr>
<th>Viscosity and its significant parameters at time = 0.</th>
<th>Mean</th>
<th>SD</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viscosity (mPa s)</td>
<td>9.339</td>
<td>2.63</td>
<td>.28</td>
</tr>
<tr>
<td>$R_p$ (kOhm)</td>
<td>.067</td>
<td>.009</td>
<td>.13</td>
</tr>
<tr>
<td>$R_i$ (kOhm)</td>
<td>.391</td>
<td>.115</td>
<td>.29</td>
</tr>
<tr>
<td>$C_m$ (nF)</td>
<td>.422</td>
<td>.073</td>
<td>.17</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>33.7</td>
<td>1.458</td>
<td>.04</td>
</tr>
<tr>
<td>Ht (%)</td>
<td>.396</td>
<td>.063</td>
<td>.15</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>3.259</td>
<td>1.210</td>
<td>.37</td>
</tr>
<tr>
<td>CRP (g/l)</td>
<td>.0093</td>
<td>.01013</td>
<td>1.09</td>
</tr>
</tbody>
</table>

SD = Standard deviation, CV = coefficient of variation.
however a significant decrease appeared already after 24 h. Mean hematocrit decreased from 42.1% to 35.4%. Fibrinogen levels increased during the 72 h observation period, reaching statistical significance at 6 h and onwards. CRP increased significantly over the 72 h observation period. The change in time plot of plasma resistance \( R_p \) was almost identical with the curve of hematocrit. The pattern as shown for intracellular resistance \( R_i \) did not reach statistical significance compared to the value at starting time. The cellular membrane capacitance \( C_m \) significantly decreased after 48 h.

### 4.4. Viscosity estimation model based on temperature and electrical impedance

Non-linear regression analysis showed the following relations to describe the blood viscosity by means of temperature and electrical impedance \( (\text{Viscosity}_{\text{imp}}) \):

\[
\text{Viscosity}_{\text{imp}} = (p_1 + p_2 R_p T) \times SR(p_3 R_i T + p_4 R_i)
\]

In this model the plasma resistance \( R_p \), the intracellular resistance \( R_i \) and blood temperature \( T \) explained almost 90% of the variance of the viscosity–shear rate relationship, as observed with the Contraves LS 300 viscosity meter. \( (R^2 = .892) \). Table 2 presents the parameters \( p_1 \)–\( p_4 \) of the blood viscosity estimation model by electrical impedance \( (\text{Viscosity}_{\text{imp}}) \). Notice that the 95% confidence intervals do not contain zero indicating that all parameters contributed significantly to the estimation of viscosity (Table 2). From the three elements impedance model only \( R_p \) and \( R_i \) significantly contributed to the estimation of blood viscosity. \( C_m \) did not contribute significantly to the viscosity estimation and was eliminated from the viscosity estimation model for that reason.

### 4.5. Viscosity estimation model based on hematocrit and the level of inflammatory proteins fibrinogen and C-reactive protein

Non-linear regression analysis showed the following relation to estimate the blood viscosity \( (\text{Viscosity}_{\text{lab}}) \) by means of hematocrit, fibrinogen and CRP:

\[
\text{Viscosity}_{\text{lab}} = (p_1 + p_2 H_t) + p_3 Fibr + p_4 H_t CRP) SR(p_5 H_t + p_6 Fibr + p_7 CRP)^2
\]

Temperature was also involved as an independent variable during evaluation of the model but did not contribute significantly to the estimation of viscosity and was left out of consideration. The variance that could be explained by hematocrit and the inflammatory proteins was similar to that calculated for the impedance model; \( R^2 = .884 \). Table 3 presents the parameters \( p_1 \)–\( p_7 \) to estimate viscosity \( (\text{Viscosity}_{\text{lab}}) \) from the blood levels of hematocrit and the inflammatory proteins.
4.6. Comparison of viscosity estimation models.

Fig. 2 shows the mean viscosity of all patients over time for all three methods of viscosity determination versus shear rate. The bars represent the 95% confidence interval of the mean. Strong dependency on shear rate for all three methods of viscosity measurement is demonstrated. The overall shear rate dependency is well described by all three methods. However, the two viscosity estimation models deviate from viscosity at high shear rates. Good agreement was observed for the clinical more relevant lower shear rates. The shear rate to present the results of Bland–Altman analysis is chosen at a shear rate of 5.5 s⁻¹. The mean viscosity measured at a shear rate of 5.5 s⁻¹ was 7.92 mPa s. The bias between the two methods of viscosity estimation is 0.04 mPa s (5%) and the limits of agreement are -1.69 mPa s (-21%) and 1.78 Pa.s (22%). The Bland–Altman plot is shown in Fig. 3(a). There was no apparent trend in the Bland–Altman plot. To further illustrate the goodness of fit from the two viscosity estimation methods to the “gold standard” Contraves viscosity, two Bland–Altman plots of laboratory versus Contraves and impedance versus Contraves are provided in Fig. 3(b) and (c).

5. Discussion

This pilot study is the first that investigated the feasibility of applying the electrical impedance technique in a central venous catheter to monitor blood viscosity on-line in human. Earlier in-vitro studies have demonstrated the relationship between electrical impedance and hematocrit and the level of inflammatory proteins (Fricke, 1953; Zhao and Jacobson, 1997; Beving et al., 1994). The impedance technique has recently also been used in other in-vitro studies related with the detection of thrombosis and inflammation (Hillebrandt et al., 2001; Abdelghani et al., 2002).

The wide range of variation in blood viscosity, temperature, hematocrit, fibrinogen and CRP in this observational study gave us the opportunity to construct two mathematical models. One from in-vivo electrical impedance measurements and the other from the major determinants of viscosity: hematocrit, fibrinogen and CRP. It is clear that the two viscosity estimation methods differ at most 2 mPa s from the Contraves viscosity (in the range of 4–13 mPa s). Note that this Bland–Altman analysis is not an external validation of the two methods on independent data, but it does show that the two methods are well able to reproduce the data that they were derived from.

The impedance model shows that plasma resistance, blood temperature and intracellular resistance all three significantly contribute to estimation of blood viscosity. From a laboratory in vitro setting it is known that cellular membrane capacity of blood (Cm) is related to hematocrit and presumably as a result of blood cell aggregation also to the level of fibrinogen and local shear rate (Fig. S5, Supplement on-line; Iliev, 2012). Most likely due to this lack of specificity the cellular membrane capacity did not contribute significantly to the estimation of blood viscosity. In contrast to Cm, blood is little known about Rl (the intracellular resistance) and its possible relation with physiological parameters. The mechanism in which Rl contributes to viscosity estimation is a subject of further research.

In earlier studies the accurate measurement of hematocrit by impedance technique using the value of ρp at 20–100 kHz has been demonstrated and nowadays point-of-care instruments for hematocrit measurement exist using the impedance technique (Steinfeld-Visscher et al., 2007). Our group has shown the accuracy of catheter-based electrical impedance measurements in-vivo for on-line monitoring of hematocrit in an animal model (Pop et al., 2004). In this study the similarity between the hematocrit values, measured in the laboratory, and the hematocrit values as reflected by ρp at 100 kHz has been confirmed. For measurement of blood viscosity, including the aggregating effect of the inflammatory proteins, the triple frequency impedance method is needed, using frequencies up to 1500 kHz (Zhao and Jacobson, 1997; Pribush et al., 1999, 2000).

Hematocrit, fibrinogen and CRP all contributed significantly to the second model of viscosity estimation. A small temperature effect on blood viscosity is described in the literature (Neumann et al., 1987). However, the described temperature effect could not contribute significantly to the estimation of blood viscosity in the hematocrit and acute phase proteins model such as developed in this study population.

Both models show an excellent fit with the shear rate dependent blood viscosity as obtained from arterial blood samples and analyzed with a calibrated high precision viscometer (Contraves LS 300). Bland–Altman analysis demonstrated a bias less than 1% and good agreement between the two estimation models, indicating that the two methods can be used interchangeably. The advantage of the impedance catheter is that it generates viscosity information continuously and can be used to monitor the critically ill patient.

The blood viscosity in this patient group with a low cerebral blood flow after cardiac arrest is the highest in the beginning and does not change significantly during the first 24 h of external cooling. The increase in acute phase proteins (CRP and fibrinogen), increasing viscosity, is counterbalanced by the effect of the lower hematocrit, decreasing viscosity. The significant rise of CRP and fibrinogen confirms the inflammatory state in these patients (Adrie et al., 2004) and it is known that this increases blood viscosity (Weaver et al., 1969; Weng et al., 1996). The statistically significant diminished hematocrit at 24 h is partially due to the haemodiluting effect of the rapid infusion of 30 ml/kg bodyweight of cold Ringer’s lactate at 4 °C. However, the decrease of hematocrit is described in literature also as a physiological reaction when a systemic inflammation occurs (Keel and Abkowitz, 2009).

The important significance of the inflammatory proteins for determination of blood viscosity is also clear from our statistical analysis, using the different laboratory parameters to estimate blood viscosity. At higher hematocrit the influence of inflammatory proteins on blood viscosity is the highest (Chien et al., 1987); at lower hematocrit the distance between red cells becomes too great for the proteins to exert their aggregating effect. The same is true for low shear conditions, when the inflammatory proteins will have more aggregating effect than in high shear conditions. Therefore, if blood viscosity indeed is an important determinant of cerebral blood flow (Grotta et al., 1982; Goslinga et al., 1992) patients after cardiac arrest with low flow conditions and higher hematocrit are at the highest risk of impaired cerebral circulation. Lowering blood viscosity by hemodilution will help and will diminish the influence of inflammatory proteins on aggregation of blood cells (Weaver et al., 1969; Weng et al., 1996).

6. Conclusion

This study demonstrates proof of principle to monitor blood viscosity continuously in the human right atrium by a dedicated central venous catheter equipped with an impedance measuring device. No safety problems occurred and there was good agreement with in-vitro measurements of blood viscosity using a standard Contraves LS 300 instrument. The performance of the model to estimate blood viscosity from electrical impedance measurements was similar to the performance of the model using hematocrit and the acute phase proteins fibrinogen and CRP to estimate blood viscosity.
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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.bios.2012.09.033.

References


